Cognitive functioning in meningioma patients

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COGNITIVE FUNCTIONING IN MENINGIOMA PATIENTS

INSIGHTS IN INDIVIDUAL TEST PERFORMANCES AND CHANGES OF PERFORMANCE AFTER SURGERY

IKRAM MESKAL

Colofon

Cognitive functioning in meningioma patients: insights in individual test performances and changes of performance after surgery
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Cognitive functioning in meningioma patients

Insights in individual test performances and changes of performance after surgery

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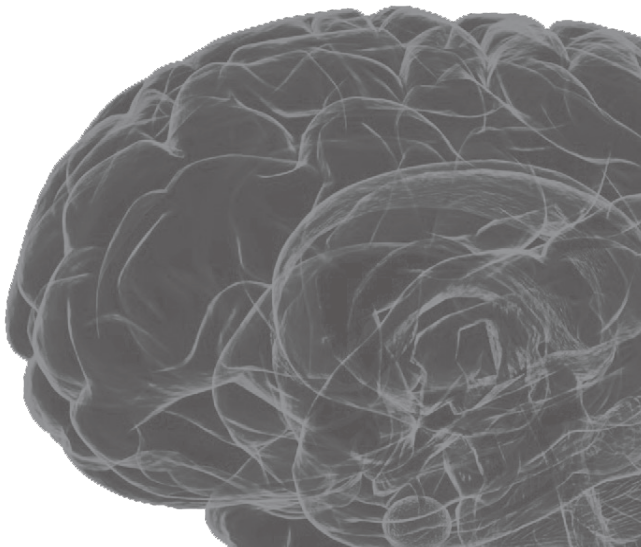
CHAPTER 1

Introduction



Primary central nervous system (CNS) tumors (including brain and spinal cord tumors) are a heterogeneous group of neoplasms originating from intracranial tissues and the meninges with degrees of malignancy ranging from benign (non-malignant) to aggressive (malignant) (1-3). The focus of this thesis is on meningiomas, that represent about one third of all tumors of the CNS (4). The exact cause of meningiomas is not well understood; associations have been found with genetic (inherited), hormonal, and environmental factors (i.e., radiation exposure) (5). Incidence increases with age and reaches its peak in the sixth and seventh decades (6). Although meningiomas are the second largest group of symptomatic primary brain tumors, incidence, epidemiology, and clinical outcomes have generally been poorly defined (7). According to the Netherlands Cancer Registry, 450 to 500 patients are diagnosed with a symptomatic meningioma each year (i.e., 1.8 per 100,000 males and 4.5 per 100,000 females) (6). Meningiomas are by far the most common incidentally found brain tumors, with estimates in the literature ranging from 1% to 3% (6). In the Netherlands it is estimated that 75,000 to 100,000 individuals have such an asymptomatic meningioma (6).

Availability of magnetic resonance (MR) imaging has facilitated the detection and diagnosis of meningiomas (8). In addition, advances in neurosurgery, anesthesiology, radiotherapy and radiosurgery have led to reduced morbidity and mortality of treatment modalities, and to better survival rates (9). As a consequence, the individual patient's quality of life and cognitive functioning are increasingly recognized as important parameters in clinical decision making.

MENINGOMA

Although meningiomas are often referred to as brain tumors, they actually arise from the meninges (more specifically, arachnoidal cells) and do not grow from brain tissue. Meningiomas typically present as slowly growing dural-based masses (10). They are classified into 3 grades according to the system of the World Health Organization (WHO) (11, 12). WHO grade I, or benign meningiomas, constitute approximately 90-95% of all meningiomas. These tumors grow slowly and have the most favorable long-term survival, although less than in the general population (12). A retrospective Dutch study found that 10- and 20-year survival in patients that were operated for a benign meningioma was respectively 81% and 53% (as compared to respectively 86% and 66% in the general population when corrected for age and sex) (6). Atypical meningiomas (grade II) and malignant meningiomas (grade III) comprise approximately 5-10% of the total, and these patients have a poorer prognosis than benign meningiomas (13). Atypical meningiomas refer to a more aggressively growing form of meningioma with brain invasion, that are more likely to recur after treatment (13). WHO grade III meningiomas, also named anaplastic or malignant meningiomas, form the smallest group. These tumors are highly invasive and often recur rapidly despite various treatments, making them cancers that are very difficult to control (6, 10). Overall survival is around 5 years (13).

TREATMENT

Neurosurgical resection is often the first choice of treatment for symptomatic meningiomas, depending on the mass effect and location of the tumor as well as surgical risks, age and medical condition of the patient (14, 15). Benefits of surgery need to be balanced against those of radiosurgery or radiotherapy, and against a watchful waiting policy. Radiotherapy is mostly reserved for meningiomas that are inoperable, or where a significant remnant was left during surgery (16). Radiotherapy is also used for recurrent meningiomas or as adjuvant treatment in grade II or III meningiomas (15, 16). Radiosurgery (e.g., with a Gamma Knife) can be a good alternative for resection in case of smaller meningiomas (maximum diameter ± 3-4 cm), and is

able to stop tumor growth in a significant number of cases (i.e., control the disease) or even cause tumor shrinkage with improvement of symptoms (17).

COGNITIVE FUNCTIONING IN PATIENTS WITH MENINGIOMA

Meningiomas can reach a considerable size before clinical symptoms appear, presumably due to their slow growth pattern and the plastic potential of the brain (i.e., the potential of the nervous system to reshape itself during ontogeny, learning or following injuries) (18-20). Depending on the size and location of the meningioma, patients may suffer from a wide variety of somatic and psychological symptoms. Common presenting symptoms are epileptic seizures, focal neurological deficits (ranging from visual disturbances to sensorimotor weakness), cognitive symptoms (e.g., memory problems, attentional problems), and psychiatric symptoms (e.g., anxiety, depression, psychosis) (21, 22). Symptoms are usually attributed to the local mass effect of the tumor, and are in some cases also explained by a general increase in intracranial pressure (22). The mechanisms through which cognitive deficits develop and progress, however, are incompletely understood. Several other causes may contribute to cognitive impairments, including tumor-related epilepsy, medication (e.g., anti-epileptic drugs, steroids), and complications of treatment (e.g., stroke after surgery or side-effects of radiotherapy) (14, 23, 24). Anxiety and depression symptoms as emotional reactions to diagnosis and prognosis may also have a negative impact on cognitive functioning in meningioma patients (25). Finally, patients' coping style can influence their emotional adjustment to diagnosis (26).

Cognitive dysfunction is a common problem in patients with primary brain tumors (1). Most studies in this area have focused on patients with gliomas i.e., primary tumors arising from the glia cells in the brain (3). Remarkably, only very limited data is available on cognitive functioning in meningioma patients, compared to the quantity of data regarding clinical and oncological outcome measures in these patients (e.g., neurological status, rate of survival, tumor recurrence, and disease progression) (24). When I started this research project, in 2012, there were hardly any studies on cognitive functioning in meningiomas. Although meningiomas are extra-axial tumors (i.e., tumors that originate outside of the actual tissues of the brain), cognitive decline may arise due to edema and mass effect on normal cerebral tissue (24). This stresses the importance of this research project, especially since cognitive deficits in meningioma patients can be subtle and can go unnoticed during neurological examination. At the time I started the review of the literature there were 11 studies that evaluated cognitive functioning in meningioma patients before and after treatment (i.e., surgery with or without adjuvant radiotherapy). Only 6 of these 11 studies reported on cognitive performance as primary outcome measure. In general these studies indicated that meningioma patients have impaired cognitive functioning both before and after surgery. Deficits were observed in various cognitive domains including memory, attention, and executive function (27). Surgery generally seemed to have a beneficial effect on cognitive function. Although a significant improvement in cognitive functioning was found 3 to 9 months after surgery (mostly on memory, attention, and executive function), cognitive performance remained on average below normal (see Chapter 3 for an extensive review on cognitive functioning in meningioma patients). All these studies thus reported cognitive outcome measures in meningioma patients at group level. Group results, however, mask response variability among individuals, and are therefore of limited use in clinical practice.

Taken together, there are many questions left regarding cognitive functioning in meningioma patients, both before and after surgery. It is largely unknown what factors determine individual long-term cognitive outcome after surgery, and more specifically what the chances are that a

patient will benefit (or not) from the procedure at the cognitive level. Answers to these questions are not only of interest from a scientific point of view, but will provide both clinician and patient with information that improves the quality of the decision-making process. For this purpose, we implemented routine cognitive testing in clinical practice for meningioma (and other neurosurgical) patients, both before and after surgery. As traditional neuropsychological testing generally takes several hours and is very labor-intensive, a brief neuropsychological assessment was therefore chosen. In recent years various computerized neuropsychological test batteries have been developed that offer an attractive alternative to the (often more lengthy) traditional neuropsychological paper-based assessment.

COMPUTERIZED COGNITIVE TESTING

Computerized neuropsychological test (CNT) batteries have become increasingly popular in clinical and research settings over the past years (28). Major advantages of CNT's include a shorter assessment time, lower costs of test administration, a more accurate measure of reaction time and less time-consuming scoring procedures (28, 29). Although current computerized testing programs are advantageous, they cannot yet fully replace the diagnostic work of a clinical neuropsychologist. For example, computers are unable to extract information gained from interaction and clinical observation, nor can they draw conclusions regarding the level of attention, motivation, or fatigue (30). However, computerized testing programs provide an adequate and time-efficient clinical technique to rapidly screen for possible cognitive deficits in patients, and are easier to implement in daily clinical care than traditional cognitive paper-and-pencil assessments (28). At the same time CNT's are much more comprehensive than for example the Mini-Mental State Examination (MMSE). Also, computerized tests facilitate administration of alternative forms of a test (with numerous combinations of randomly presented test stimuli) which mitigate practice effects (28). They can quickly provide a fully automated calculation and presentation of the results (in terms of raw scores as well as standardized scores related to normative data), which can be included into summary reports automatically (28, 29). Therefore, such a screening instrument seems very promising for clinical purpose in meningioma patients.

One such computerized neuropsychological battery is the Central Nervous System Vital Signs (CNS VS (28)), which is a battery that has been translated into over 50 languages including Dutch (http://www.cnsvs.com). In contrast to other computerized batteries, for which new tests were developed, CNS VS is composed of tests which are mostly based on well-established conventional paper-and-pencil tests (28). CNS VS has been shown to be well suited for use as a brief clinical screening tool for cognitive dysfunction in different patient groups such as patients with mild cognitive impairment and dementia, post-concussion syndrome and severe traumatic brain injury, (treated and untreated) ADHD, and (treated and untreated) depression (28). It comprises 7 neuropsychological tests, with measures of performance in 11 cognitive domains (i.e., composite memory, verbal memory, visual memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, executive function, simple attention, and motor speed). Since some domains scores generated by CNS VS are very similar and show considerable overlap with other domains of the battery (i.e., mainly calculated based on components of the same tests), not all 11 cognitive domains will be considered in this study. Administration lasts 30-40 minutes and the presentation of stimuli is randomized in order to minimize practice effects. Raw scores include total numbers of correct or incorrect responses, reflecting accuracy, and mean reaction times (in milliseconds) on individual tests and domains, reflecting speed. Normed scores are

automatically generated by CNS VS and represent the performance of an individual relative to the American normative sample corrected for age (N = 1,069+ (28)).

The studies presented in this thesis employ CNS VS in order to evaluate cognitive functioning in patients with meningioma before and after surgery. Setting up this research project properly took a large amount of time and planning effort (e.g., approval by the medical ethical committee, embedding neuropsychological assessments before and after surgery within routine clinical care for meningioma patients, etc.). The department of Neurosurgery of the Elisabeth-TweeSteden Hospital (Tilburg, The Netherlands) together with the department of Cognitive Neuropsychology of Tilburg University has developed a protocol for computerized neuropsychological testing in which brain tumor patients admitted for surgical resection underwent neuropsychological assessment 1 day before surgery and 3 months after surgery as part of standard clinical neuro-oncological care. A 12 months post-operative follow-up assessment was added later (January 2014) for research purposes in order to explore long-term cognitive functioning. At the start of this research project, we evaluated the use of the CNS VS battery as a brief clinical tool for screening for cognitive dysfunction, as (the formal Dutch translation of) this tool had not been used before in a Dutch neurological patient sample. Patients suffering from trigeminal neuralgia (TN; a severe chronic facial pain disorder) were assessed with CNS VS (10) 1 day before surgical microvascular decompression (MVD; a procedure that requires a craniotomy and frees the root of the trigeminal nerve from compression of an artery). Thus, similar to brain tumor patients, patients suffering from TN undergo a craniotomy procedure under general anesthesia with the difference that MVD for TN does not require an operation into the brain tissue. Since the largest neurocenter of the Netherlands is located in the Elisabeth-TweeSteden Hospital, we had access to a relatively large group of these patients. In addition, no information was available on cognitive performance in TN patients as no prior studies had been conducted, which prompted us to start our research project with this particular patient group.

AIMS AND OUTLINE OF THE THESIS

The aim of this thesis is to evaluate cognitive functioning in meningioma patients, and, more specifically to gain new insights in individual test performances and changes of performance after surgery. In addition, this thesis also aimed to evaluate computerized testing as a clinical instrument to detect cognitive impairment in meningioma patients. **Chapter 2** presents a systematic review on cognitive functioning in meningioma patients. We evaluated relevant findings and methodologic aspects of studies on cognitive functioning in meningioma patients before and after surgery with or without adjuvant radiotherapy. In **Chapter 3** we evaluated the first-time use of the formal Dutch translation of the CNS VS battery as computerized clinical neuropsychological screening tool for cognitive function in a (Dutch) neurological patient population (N = 32). In addition, this was the first study on cognitive function in patients with TN (N = 32). For the purpose of this study we compared patients' cognitive performance with performance of 2 control groups of healthy subjects: the normative American data from the CNS VS database and a group of Dutch healthy individuals that we recruited ourselves, in order to evaluate the application of the normative data and also the formal translation in Dutch of CNS VS to the Dutch population. **Chapter 4** reports on the clinical application of CNS VS in meningioma patients (N = 68). This was the first prospective study on cognitive function in patients with meningioma and it investigated the incidence and severity of cognitive dysfunction in 68 meningioma patients before and 3 months after surgery, and the change in dysfunction over time, both at group and individual patient level. All patients were assessed with CNS VS and compared to its published normative data. In **Chapter 5** we

compared the normative data of CNS VS to a new large Dutch sample (N = 158), since the data of the CNS VS battery are based on the American population that were solely corrected for age and had also been collected over a decade ago. **Chapter 6** describes individual changes in cognitive performance over time and predictors of late cognitive functioning in meningioma patients 12 months after surgery by using socio-demographically adjusted normative formulae for the Dutch population, based on CNS VS resulting from the study described in Chapter 5. Finally, **Chapter 7** provides a summary and a general discussion. Methodological strengths and weaknesses of the studies are considered. This thesis concludes with suggestions for clinical practice and future research.

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CHAPTER 2

Cognitive functioning in meningioma patients: a systematic review

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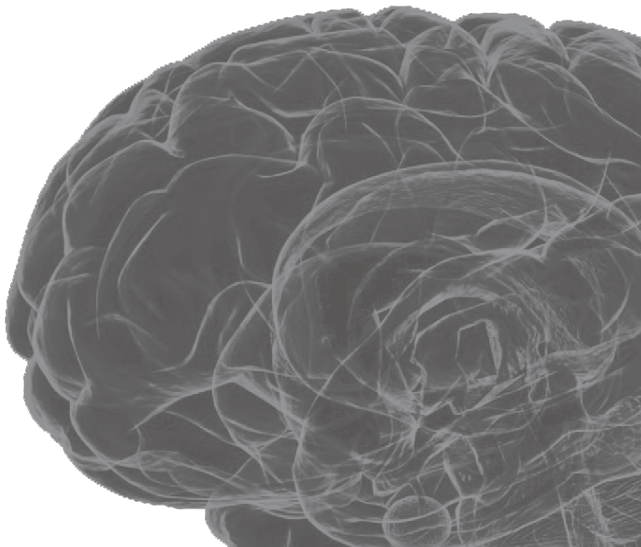

INTRODUCTION

As a result of increasingly effective disease management, patients with brain tumors have better survival rates. This prompts a different approach towards health care. Instead of considering survival as the sole endpoint, quality of survival is also considered (1). The assessment of health related quality of life (HRQoL) and cognitive function has become increasingly recognized as an important outcome measure in brain tumor research. Cognitive functioning has a significant impact on HRQoL, and could even be a predictor of HRQoL (2).

To date, most studies on cognitive functioning in brain tumor patients have focused on glioma patients. Less is known about cognitive functioning in meningioma patients and the impact of surgery and/or (adjuvant) radiotherapy (3-10). Rapidly growing tumor types such as high-grade gliomas typically lead to more cognitive impairment than slowly growing tumors such as meningiomas (11, 12). However, even meningiomas can cause cognitive deficits by putting pressure on brain tissue (13). These tumors often grow to a considerable size before clinical symptoms appear because of the plastic potential of the brain (14-17).

The objective of this systematic review was to evaluate the available data and the quality of studies on cognitive impairment in meningioma patients prior to and/or following treatment, and to document potential changes in cognitive dysfunction due to treatment (i.e., surgery with or without adjuvant radiotherapy). We also reviewed methods used to evaluate cognitive function in meningioma patients, and make recommendations for future studies.

METHODOLOGY (SYSTEMATIC REVIEW)

Inclusion criteria

This systematic review included peer-reviewed research articles on cognitive functioning in adult patients with meningioma prior to and/or following surgery with or without adjuvant radiotherapy, as assessed with neuropsychological tests.

Search strategy

Searches were conducted using the electronic databases of PubMed (MEDLINE) and Web of Science (Web of Knowledge). For each database, searches included the terms: mening* or brain or cerebral or cranial (title/abstract, topic), in addition, an 'and' condition was specified for the following 2 groups of terms: (1) neuropsycholog* or cognit* or neurocognit* or attention* or memory or executive function* (title), (2) tumor* or tumour* or neoplasm* (title). Searches were limited to adult human-beings and peerreviewed original research papers written in English. In addition, results of studies that examined cognitive functioning in groups of brain tumor patients were also included if separate analyses were done for meningioma patient groups. Studies without objective measures of cognitive function as assessed with neuropsychological tests were excluded. Studies that used very short screening tests, such as Mini-Mental State Examination (MMSE) and 3MS examination (modified MMSE) were included, but are only briefly discussed. There were no restrictions on publication dates, and the final searches were done in December 2015.

Study selection process

In total, 2205 article citations (i.e., 873 in PubMed + 1332 in Web of Science) were found and downloaded into EndNote (18). These were scanned using EndNote for duplicates, and 1193 were deleted, yielding a final total of 1012 articles.

Then, the titles of these articles were sifted to exclude all articles that did not meet the objectives of this review, which resulted in the removal of 886 articles. This first sift resulted in 126 articles for which abstracts and/or full text articles were assessed in detail. Subsequently, 115 (out of 126) articles were rejected because they did not meet the inclusion criteria, were conference presentations or case reports. The remaining 11 articles were examined jointly by 2 reviewers and remained included for this review.

RESULTS

Table 1 summarizes the 11 studies that evaluated cognitive functioning in meningioma patients prior to and/or following treatment. In this section, results from studies including pre-operative and post-operative cognitive assessments are discussed. The effects of adjuvant radiotherapy on cognitive outcomes are discussed in a subsequent section. Potential associations of cognitive impairment with tumor location and other factors are presented in Box 1.

Cognitive functioning in meningioma patients prior to and/or following surgery

Cognitive functioning prior to treatment was examined in 5 studies with a total of 199 meningioma patients eligible for surgery (4, 7, 10, 19, 20) (see Table 1). Overall, in these studies, cognitive functioning has been found impaired. Most commonly affected domains were memory, attention, and executive functions. Cognitive functioning following surgery was investigated in 7 studies including a total of 302 meningioma patients (4, 7-10, 19, 20) (see Table 1). All studies, except 2 (8, 9), started with a pre-operative assessment. Pre-operative assessments allow to determine possible effects of surgery on cognitive performance. Only 2 (4, 20) of the 5 studies with a repeated (pre-and post-operative) assessment of cognitive function controlled for the influence of practice effects. In general, all studies showed significant improvements following surgery in cognitive functioning, mostly on memory, attention, and executive function. There was no consistency in results across studies with regard to the cognitive domains that did not improve after surgery. However, despite cognitive improvements, all studies (including those without pre-operative assessment) demonstrated that patients (still) had significantly lower scores on various cognitive domains after surgery, compared to healthy controls. For studies including a pre-and post-operative assessment (mean interval between 2 assessments ranging from 3 to 9 months), no clear conclusions can be drawn on the effect of time since surgery on the post-operative cognitive outcome. Severity data (e.g., effect sizes, incidences) were not available for most of them, due to differing populations.

In particular, Tucha and colleagues (4) found significant pre-operative impairments in patients with frontal meningiomas (N = 54) on measures of working memory, attention, and executive functions (lower mean raw scores, longer reaction times, or higher error rates), compared to healthy controls (matched for age, gender, educational level, handedness, and intelligence). After surgery, significant improvements were observed on measures of memory and attention. However, despite these significant improvements, patients' post-operative status remained significantly impaired on attention and executive functions, compared to healthy controls who were retested over the same intervals. According to the authors, only the better post-operative performance on figural memory (immediate recall) could be partly explained by practice effects by comparing the test results with the healthy control group. Note that the authors classified flexibility and shifting as subdomains of attention. However, these measures can also be considered as components of executive functioning (21). In addition, Tucha and colleagues (10) conducted a study with elderly meningioma patients (N = 33). These patients showed significant pre-operative impairments on

measures of working memory, short-term figural memory, attention, and executive functions (lower mean raw scores, longer reaction times, or higher error rates), compared to healthy controls in the same age-range. After surgery, significant improvements were observed on measures of memory and attention, with the exception of working memory. In this study, patients' post-operative cognitive status corresponded with the cognitive functioning of the healthy control group (except for working memory). Because the healthy controls were only tested once, it was not possible to rule out practice effects, which may have masked lower performance in the elderly meningioma patients. See the above-mentioned note regarding the classification of cognitive domains by these authors. It was not reported if there was overlap in patients between these 2 studies by Tucha and colleagues; a certain amount of overlap between the patient samples seems possible (4, 10).

In a recent study by Meskal and colleagues (20), meningioma patients (N = 68) had significantly lower mean pre-operative and post-operative standard scores on measures of memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, and executive functioning, compared to (American) normative data as provided by the Central Nervous System Vital Signs battery (i.e. CNS VS), a brief (30 min) computerized battery of neuropsychological tests (22). Forty-seven out of 68 patients (69%) scored low or very low on 1 or more cognitive domains. After surgery, significant improvements were observed on all cognitive domains, with the exception of psychomotor speed and reaction time. Twenty-seven out of 62 patients (47%), scored low or very low on 1 or more cognitive domains after surgery.

The 3MS test used in a study by Yoshii and colleagues (7) showed a subnormal function (mean 3MS score < 85) in 34 meningioma patients pre-operatively. Cognitive function normalized after surgery only in patients with right-sided (N = 17) meningioma (post-surgery mean 3MS score > 85). Note that the authors have chosen for a more stringent cut-off of 85 instead of 77/78, which is generally used as cut-off for cognitive impairment (23). In addition, patients were tested within 1 month after surgery, which is a very short follow-up time that may identify (more severe) transitory cognitive problems instead of persistent cognitive deficits in left-sided meningioma patients. Furthermore, it was not clearly described by the authors why some patients had only 1 assessment (i.e., prior to, or following surgery), and other patients were assessed twice with the 3MS test (prior to, and following surgery).

Another study, by Koizumi and colleagues (19), evaluated cognitive dysfunction with the MMSE in meningioma patients (N = 10) who also underwent ^{123}I-Iomazenil (IMZ) single-photon emission computed tomography (SPECT) imaging. The mean pre-operative MMSE scores were 19.9 ± 11.4; ranging from 2 to 30. The MMSE cutoff points for normal, mild, moderate, and severe cognitive impairment were not described by the authors. Based on the MSSE cut-off levels application by Folstein and colleagues (24), 3 patients had moderate to mild cognitive impairment (scores on MMSE ranging from 20 to 25), and 3 patients had severe cognitive impairment (scores ranging from 2 to 5); 4 of them had scores of 29–30. Overall, 6 patients scored above the cut-off point of 23. After surgery, a significant improvement in cognitive function (mean post-surgery MMSE: 26.5 ± 3.8) was found. Seven of the 10 patients scored above the cut-off of 23 on the MMSE, which suggests 'normal' cognitive functioning in those patients. Note that screening tests such as the MMSE and 3MS are not sensitive enough to discriminate between mild cognitive impairment and normal cognitive functioning (25).

Van Nieuwenhuizen and colleagues (6) found significantly lower mean Z-scores in patients with a wait-and scan policy = 21) on measures of psychomotor speed and working memory, compared to normative matched healthy controls from the Maastricht Aging Study (i.e., MAAS (26)). Note

that this study was conducted in a specific group of meningioma patients, in which the tumor was small, growing slowly, and was not causing symptoms or if surgery carried too many risks, particular for older patients who are more vulnerable to develop complications after surgery due to their medical condition.

Steinvorth and colleagues (27) included 10 patients admitted only for fractioned stereotactic radiotherapy (FSRT) instead of surgery. However, the authors did not report cognitive results. Note that the patients who were included in the studies by Van Nieuwenhuizen and colleagues (6) and Steinvorth and colleagues (27) were substantially different (e.g., smaller tumor volumes, inoperable meningiomas after subtotal resection or recurrence) from those patients who were admitted for surgical treatment. Therefore, the results of the aforementioned 2 studies cannot be generalized to the general population of meningioma patients admitted for surgery.

In another study by Van Nieuwenhuizen and colleagues (8) in which some (N = 18) meningioma patients were tested only after surgery and not before, significantly lower mean standard scores were found on a number of verbal memory subtests, compared to normative healthy controls. The authors concluded that these patients had significantly lower cognitive functioning than healthy controls. Attention and executive function were not impaired in these patients. The patients of this study were compared with patients (N = 18) who received adjuvant radiotherapy after surgery (RTx+). The results of the latter patient group are discussed in the section on effects of adjuvant radiotherapy. It should be noted that although overlap in patients between this study and the above-mentioned study of Van Nieuwenhuizen cannot be ruled out, this is not likely since the study in patients who had already undergone surgery (8) preceded the study in patients in whom surgery was not performed (6).

Similar to the aforementioned study, Krupp and colleagues (9) investigated cognitive functioning after surgery without a pre-operative assessment in 91 patients. Compared with published normative population values, major deficits in attention appeared in patients of approximately 55 years of age, worsening in patients with increasing age. Significant negative correlations were found between age and attention performance in patients older than 55, as well as with the intelligence factors verbal knowledge, technical ability, and word fluency. No such correlation was found for reasoning and age. Since no pre-treatment assessment was available in the aforementioned 2 studies, the specific effects of the brain tumor or surgery on cognitive performance cannot be determined.

Cognitive functioning in meningioma patients: effects of adjuvant radiotherapy

Three studies investigated cognitive functioning in meningioma patients who had undergone radiotherapy after surgery (2, 5, 8). These studies described the same (2, 5). or an overlapping (8) patient sample, but investigated different types of research questions. In these studies, patients in whom the tumor could only be partially resected and patients with a recurrence after surgery received adjuvant radiotherapy.

The study by Van Nieuwenhuizen and colleagues (8) investigated the exclusive effects of adjuvant radiotherapy after surgery by comparing patients who had surgery only (RTx-) with patients who had surgery and adjuvant radiotherapy (RTx+). The authors found no significant differences in mean standard scores on all cognitive measures (memory, attention, executive function, and perception) between RTx- (N = 18) and RTx+ (N = 18) patients (which may be patients with different tumor characteristics). No comparisons were made for cognitive functioning between the RTx+ group and healthy controls. In this study, additional radiotherapy did not have deleterious effects on cognitive functioning. The studies by Dijkstra and colleagues (5) and Waagemans and

colleagues (2) did not differentiate between the effects of surgery and/or radiotherapy. In the study by Dijkstra and colleagues, patients (N = 89) showed significantly lower mean *Z*-scores on measures of verbal memory, visual memory, working memory, information processing, psychomotor speed, and executive function (most impaired), compared to normative matched healthy controls (from MAAS (26)). No significant differences were found for attention. Note that the proportions of patients with cognitive deficits (defined as 1.5 *SD* below the mean of a matched control group) was not reported by these authors. The study by Waagemans and colleagues (2) focused on HRQoL and reported similar findings on cognitive functioning in meningioma patients (N = 89) as in the study by Dijkstra and colleagues (5). A common limitation of the aforementioned studies was an absence of a pre-treatment assessment of cognitive functioning. Also noteworthy is the large standard deviation (*SD*) of tumor volumes in these studies.

Only 1 study (27) investigated the effects of FSRT following surgery in meningioma patients (N = 30). In this study, cognitive function was evaluated before and after FSRT. Patients had normal mean percentile scores, except for a slow information processing speed prior to radiotherapy. After the first fraction, a transient decline in memory and, at the same time, improvements in attentional functions were observed. No deteriorations were seen during the further follow-up, but further increases in memory and attention were observed. Note that the improvement in attention was considered as a practice effect, since a comparable improvement was also observed in a control group, included in an earlier report by these authors (27).

Table 1 Studies on cognitive functioning in meningioma patients

Study	Patient group	Control group	Treatment	NP tests/domains	Timing of assessment(s)	Definition of CI	Statistics	Relevant results prior to treatment	
Tucha, 2003 (4)	54 ST frontal MGM Grade[1]=NR M age=57.8 (*SD* = 1.5) M vol=79.3 cm (*SD* = 11.3)	54 matched HC M age=57.9 (*SD* = 1.5)	Surgical removal	VerM, VisM, Att, EF, VC	2-3 days before surgery, 4-9 months after surgery	None	Non parametric tests, Ipsative scores[2], Spearman rank corr	Sign lower mean raw scores, longer reaction times, or higher error rates on Att and EF. Sign improvements on measures of (immediate recall) VisM and Att.	Sign lower mean raw scores, longer reaction times, or higher error rates on measures of WM, Att, and EF.
Tucha, 2001 (10)	33 ST MGM Grade=NR M age=72.8 (SEM=0.9) M vol=NR 7 tumors diameter ≤4 cm 26 tumors diameter >4 cm	20 HC M age=73.1 (SEM=1.0)	Surgical removal	Same as in (4)	Before surgery, 3-6 months after surgery	None	(Non) parametric tests	Sign lower mean raw scores, longer reaction times, or higher error rates on measures of WM, (short-term) VisM, Att, and EF.	Sign improvements on measures of (short-term) VisM and Att. Comparable post-op cogn status to cogn functioning of elderly HC, except for WM.
Meskal, 2015 (20)	68 ST and IT MGM Grade I M age=55.7 (range=36-74) M vol=NR Maximum diameter=4.38 cm	Norms based on healthy American population (22) (N = 1,069)	Surgical removal	Mem, PsyMo, RT, Att, Cog-Flex, ProcSp, EF (computer tests)	1 day before surgery, 3 months after surgery	Standard scores ≥1.5–2 *SD* below norm	T-tests, Mc Nemar's tests, Pearson product-moment corr	Sign lower standard scores on all cogn domains. 47/68 pts (69%) low or very low on 1 or more cogn domains.	Sign improved mean standard scores for all cogn domains, except PsyMo and RT. Sign lower mean standard scores for all cogn domains. 27/62 pts (47%) low or very low on 1 or more cogn domains.
Yoshii, 2008 (7)	34 MGM Grade=NR Right-sided: M age=64 (*SD* = NR) Left-sided: M age=59 (*SD* = NR) M vol=NR 83 glioma	Normative healthy population values from manual (reference: could not be retrieved)	Surgical removal	3MS test	Before surgery and/or within 1 month after surgery	Subnormal cogn function= 3 MS score<85	NR	Subnormal cogn function. No differences in cogn function between left-sided and right-sided MGM.	Normalization only in right-sided group, not in left-sided group.

Table 1 Continued

Study	Patient group	Control group	Treatment	NP tests/domains	Timing of assessment(s)	Definition of CI	Statistics	Relevant results prior to treatment	Relevant results following treatment
Koizumi, 2014 (19)	10 ST MGM Grade I: (N = 9), grade II: (N = 1) M age=68.1 (*SD* = 13.1) M vol=89.1 ml (*SD* = 51.8)	Normative healthy population values (reference: NR)	Surgical removal	MMSE IZM-SPECT	Within 4 weeks before surgery, 3 months after surgery	MMSE score≤23	NR for MMSE data, T-tests for IZM-SPECT data	Mean MMSE scores=19.9 (*SD* = 11.4), ranging from 2 to 30.	Sign improvement of cogn function, mean MMSE score=26.5 (*SD* = 3.8).
Van Niewenhuizen, 2013 (6)	21 untreated MGM, wait-and-scan approach Grade I M age=63.4 (*SD* = 13.5) M vol=6.3ml (*SD* = 6.5)	21 normative matched (age, gender, education) HC from MAAS (26) (N = 2,000), M age=62.4 (*SD* = 12.9)	None	VerM, WM, Att, EF, PsyMo, InfPro	Once	*Z*-scores ≥1.5 *SD* below norm	Mann-Whitney U-tests, Kendall's Tau	Sign lower mean *Z*-scores on WM and PsyMo, sign better mean *Z*-scores on VerM.	NAp
Steinvorth, 2003 (27)	40 ST MGM Grade=NR M age=55 (*SD* = 14) M vol= NR 1 total resection: (N = 16), 1 partial resection: (N = 8), ≥2 resections: (N = 6), no resection: (N = 10)	Normative healthy population values from manuals	FSRT	VerM, VisM, Att, IQ	1 day before FSRT, within 24 hrs after first fraction, at end of FSRT, 6 weeks, 6 and 12 months after FSRT	None	(Non) parametric tests	Sign lower mean pct scores on Att/InfPro.	After first fraction: transient decline in Mem and improvements in Att During further follow-up: no deteriorations, but further improvements in Mem and Att.
Van Niewenhuizen, 2007 (8)	36 ST MGM Grade I 18 RTx+: surgery and RTx M age=63.3 (*SD* = 10.6) M vol=39.4 ml (*SD* = 43.5) 18 RTx-: surgery only M age=62.6 (*SD* = 11.8) M vol=23.5 ml (*SD* = 19.3)	18 normative matched (age, gender, education) HC from MAAS (26) (N = 2,000) M age=NR	Surgical removal with (RTx+) /without (RTx-) adjuvant RTx	Mem, Att, EF, Perc	≥1 year after surgery	None	Chi-square tests, T-tests	NAp	No sign differences in mean standard scores on all cogn domains between RTx- and RTx+. Sign lower mean standard scores on all cogn domains in RTx-. No comparisons were made for cogn functioning between RTx+ group and HC.

Table 1 Continued

Study	Patient group	Control group	Treatment	NP tests/domains	Timing of assessment(s)	Definition of CI	Statistics	Relevant results prior to treatment	Relevant results following treatment
Krupp, 2009 (9)	91 ST MGM Grade I M age=56 (*SD* = 10) M vol=NR	Normative healthy population values from manuals	Surgical removal	Tests of Att, IQ	10-18.5 months after surgery	None	T-tests, Chi-square tests, ANOVA, Spearman rank corr, Regression analyses	NAp	Negative corr between age and Att in pts > 55 yrs, as well as with IQ factors verbal knowledge, technical ability, and word fluency.
Dijkstra, 2009 (5)	89 ST MGM Grade I M age=58.6 (*SD* = 12.1) M vol=46.1 ml (*SD* = 51.8)	89 normative matched (age, gender, education) HC from MAAS (26) (N = 2,000) M age=58.3 (*SD* = 13.3)	Surgical removal with (N = 22)/ without adjuvant RTx (N = 67)	VerM, WM, Att, EF, PsyMo, InfPro	≥1 year after surgery	*Z*-scores ≥1.5 *SD* below HC mean	T-tests, Multiple regression analyses	NAp	Sign lower mean *Z*-scores on all domains, except for Att.
Waagemans, 2011 (2)	89 ST MGM Grade I M age=58.4 (*SD* = 13.2) M vol=46.1 ml (*SD* = 51.8)	89 normative matched (age, gender, education) HC from MAAS (26) (N = 2,000) M age=58.3 (*SD* = 13.3)	Surgical removal with (N = 22)/ without adjuvant RTx (N = 67)	Same as in (5)	≥1 year after surgery	*Z*-scores ≥1.5 *SD* below HC mean	T-tests, Multiple regression analyses	NAp	Same population as in (5). Similar findings on cogn functioning as in (5).

Abbreviations: ANOVA=analyses of variance. Att=attention. CI=cognitive impairment. CogFlex=cognitive flexibility. Cogn=cognitive. Corr=correlation. EF=executive function. FSRT=fractioned stereotactic radiotherapy. GL=glioma. HC=healthy controls. IZM-SPECT=^{123}I-iomazenil (IMZ) single-photon emission computed tomography (SPECT) imaging. IT=infratentorial. M=mean-MAAS=Maastricht Aging Study (26). Mem=memory. MGM=meningioma. MMSE=mini-mental state examination. Nap=not applicable. NR=not reported. Pct=percentile. Perc=perception. Post-op=post-operative. ProcSp=processing speed. PsyMo=psychomotor speed. Pt(s)=patient(s). RT=reaction time. RTx=radiotherapy. *SD* = standard deviation. Sign=significant. ST=supratentorial. VC=visuoconstructive abilities. VerM=verbal memory. VisM=visual memory. Vol=tumor volume. WM=working memory.
3MStest=modified mini-mental state exam.
[1]Grade based on the World Health Organization (WHO) classification.
[2]These results were not reported in the review. Ipsative scores=substraction post-operative testscores from pre-operative test scores.

Box 1 Tumor location and other relevant factors related to cognitive performance prior to and/or following treatment

Relevant factors	Relevant findings	Study
Tumor location	.No sign differences in cognitive status between lateralization groups prior to and following surgery. .Sign differences in changes over time between lateralization groups, mainly on attentional functions. Left-sided (N = 22) MGM improved sign on flexibility and shifting. Right-sided (N = 21) MGM improved sign on variety of attentional functions. .Sign effect of frontal MGM on pre-operative and post-operative cognitive status. Prior to surgery; falx cerebri (N = 14) performed sign better on figural fluency than frontobasal (N = 19) and convexity (N = 17) MGM. Following surgery; frontobasal (N = 19) and falx cerebri (N = 14) MGM performed sign better on divided attention and figural memory than convexity (N = 17) MGM. .Sign differences between localization groups for various cognitive domains. Convexity (N = 17) MGM: only improvement on flexibility and shifting (attentional/executive functions), frontobasal (N = 19) MGM: improvement on a broader range of attentional/executive functions after surgery. Pts with falx cerebri (N = 14) MGM improved on various cognitive domains.	Tucha (2003) (4)
	.No sign differences in cognitive status between lateralization groups prior to and following surgery. .No sign associations between tumor lateralization and cognitive improvement over time. .No sign differences in pre-operative or post-operative cognitive functioning based on tumor localization, except for complex attention: sign better performance for infratentorial (N = 7) as opposed to supratentorial (N = 61) tumors. .No sign associations between tumor localization (skull base, convexity, and convexity/falx) and cognitive improvement over time.	Meskal (2015) (20)
	.Cognitive function normalized in right-sided (N = 17) MGM following surgery. Left-sided (N = 17) MGM did not normalize or improve. .No statistical tests were conducted in this study: no clear conclusions can be drawn.	Yoshii (2008) (7)
	.No reports on specific localization or lateralization effects on cognitive functioning. .Based on data in a table; 3 pts with very low scores (<10) on MMSE before surgery, suffered from convexity (N = 4) MGM. These pts improved substantially after surgery, but still had the lowest scores on MMSE (≤ 23), compared with other localization groups.	Koizumi (2014) (19)
	.No clear associations of memory functions with localization before FSRT (no data reported). .No clear lateralization effects before and after FSRT.	Steinvorth (2003) (27)
	.Pts with left-sided (N = 37) MGM performed sign worse on verbal memory compared to right-sided (N = 25) MGM. .Lower cognitive performance in skull-base (N = 24) MGM on verbal memory, information processing, and psychomotor speed compared to convexity (N = 28) MGM. Not clear as to whether theses analyses were done in smaller subgroups of the study sample.	Dijkstra (2009) (5)

Box 1 Continued

Relevant factors	Relevant findings	Study
Epilepsy	.Sign negative correlation between epilepsy burden and executive functioning, primarily due to AEDs use, not to epileptic seizures. .Sign impaired cognitive functioning also in pts who did not use AEDs (N = 66) compared with HC.	Dijkstra (2009) (5)
	.Comparable HRQoL in pts to that in HC. .HRQoL worse in pts with cognitive deficits and pts who use AEDs, irrespective of seizure control.	Waagemans (2011) (2)
Mood	.No sign correlation between anxiety and cognitive domains, negative correlation between depression and 6/7 cognitive domains prior to surgery (N = 60 out of 68). .Negative correlation between anxiety and attention, negative correlation between depression, memory and attention following surgery (N = 52 out of 62).	Meskal (2015) (20)
	.Sign improvement toward a positive mood from baseline (no data reported) up to 6 weeks after follow-up of FSRT. No correlations were investigated.	Steinvorth (2003) (27)
Quality of life	.RT+ pts lower HRQoL than RT- pts. .No sign differences in HRQoL between RT- pts and HC. After correction for duration of disease, no sign differences in HRQoL between both MGM groups. .No comparisons were made for HRQoL between RT+ pts and HC.	Van Nieuwenhuizen (2007) (8)
	.No sign differences between pts and HC on 7/8 HRQoL scales. .Impaired executive functioning had a direct negative relationship with other cognitive domains (information processing, verbal memory, psychomotor speed, and attention), and an indirect negative relationship with HRQoL.	Waagemans (2011) (2)
Other factors	.IZM-SPECT images showed recovered binding potential of IZM following surgery.	Koizumi (2014) (19)

Abbreviations: AEDs=anti-epileptic drugs. FSRT=fractioned stereotactic radiotherapy. HC=healthy controls. HRQoL=health-related quality of life. IZM-SPECT=^{123}I-iomazenil (IMZ) single-photon emission computed tomography (SPECT) imaging. MGM=meningioma. MMSE=mini-mental state examination. Pts=patients. RT=radiotherapy. Sign=significant.

CONCLUSION AND RECOMMENDATIONS

This systematic review provides an overview of studies investigating cognitive functioning in meningioma patients prior to and/or following surgery with or without adjuvant radiotherapy. Drawing conclusions from studies and comparison of results between them were complicated by several methodological limitations, such as a lack of pre-treatment assessments, variations in the number and types of neuropsychological tests used, definitions of cognitive impairment, quality of normative data, and absence of control for practice effects.

Specific effects of treatment cannot be determined in the absence of an assessment before treatment. The number of patients with above average cognitive abilities before treatment may be underestimated. Patients may have a functional decline, but still perform within normal ranges on cognitive tests. In addition, cognitive deficits that have been present before treatment may be unjustly attributed to surgery. None of the studies described the presenting symptoms of the meningioma patients included. Therefore, it is not clear if cognitive complaints were present at neuropsychological assessment. As the cognitive status of patients with incidentally-detected meningiomas is likely to differ from that in patients presenting with cognitive complaints, it is not clear as to whether the samples were representative of all meningioma patients.

In addition, the number and types of neuropsychological tests used, varied across studies and complicated comparison of results. For example, 8 studies (2, 4-6, 8-10, 27) tested patients with a traditional neuropsychological battery that consisted of 2 to 12 paper-and-pencil tests. One study used a computerized screening battery (i.e., CNS VS (22)) consisting of 7 neuropsychological tests (20). Two studies (7, 19) used very global screening tests (i.e., MMSE and 3MS), that are known to have a low sensitivity and are not useful for screening for subtle cognitive impairment (25).

Quality of normative data also differed between studies, 2 studies included their own healthy control group matched on different variables (4, 10), 4 studies used normative matched data from 18 to 89 healthy controls from the Maastricht Aging Study (MAAS (26)) (2, 5, 6, 8), and 5 studies used (published) normative healthy population values as provided by the test (manual) (7, 9, 19, 20, 27).

Further, definitions used to classify patients as having cognitive impairment differed across studies. Three studies (2, 5, 6) used *Z*-scores and defined individual cognitive impairment as 1.5 *SD* below the mean of a matched control group. One study (20) defined standard scores of 1.5 and 2 *SD* below the mean of a normative control group as cognitive impairment. Five studies (4, 8-10, 27) did not use a definition of individual cognitive impairment. None of the studies reported a cut-off for (general) cognitive impairment on the number of tests required to be in an impaired range. Only 1 study (20) reported on the incidence and severity of cognitive impairment.

Finally, only 2 (4, 20) of the 5 studies with a pre-and post-treatment assessment considered the influence of practice effects on improved cognitive function after repeated testing by including a (matched) control group that was tested twice with the same test battery. The computerized test battery CNS VS is assumed to be suitable for repeated testing because of the random presentation of stimuli (20, 22). However, despite the chance that a patient gets the same stimuli twice is negligible, there still could be a learning effect of the battery in general, also known as test-wiseness (28). The patient knows what to expect the second time. Thus, longitudinal studies without consideration of practice effects may report better results due to repeated exposure to neuropsychological testing. Practice effects may therefore mask cognitive decline or stability.

Moreover, many studies reviewed here lacked a clear description of statistical testing, or only very basic statistical analyses were conducted. For example, some studies only performed

univariate analyses where no correction for potential other differences between groups was applied when comparing effects of tumor localization (among groups).

To overcome some of the methodological issues described, we recommend using a test battery with a wide range of neuropsychological tests that is sensitive enough for identifying subtle cognitive impairment in patients and suitable for serial repetition. In addition, a pre-treatment assessment, a sufficiently large sample size to conduct (multivariate) analyses, a uniform definition of cognitive impairment, and appropriate quality of normative data are suggested.

Despite these limitations, the studies in this review demonstrate that meningioma patients have impaired cognitive functioning prior to treatment. In general, most commonly affected domains were memory, attention, and executive functions. Surgery generally had a beneficial effect on cognitive function. A significant improvement in cognitive functioning was found 3 to 9 months following surgery, mostly on memory, attention, and executive function. Cognitive performance still remained below normal however. There is no consistency across studies about the domains that did not improve after surgery. In the one study on adjuvant radiotherapy, no additional deleterious effects on cognitive functioning at least 1 year after surgery were found. Two other studies found that the use of AEDs negatively affects cognitive functioning and HRQoL.

Mixed findings were reported with respect to effects of lateralization and localization of the tumor on cognitive impairment. In most studies, associations between cognitive functioning and other tumor characteristics (i.e., volume, edema) were not observed (2, 4, 5) or could not be made because of the small sample sizes in the studies (6). Other factors that are known to have a relation to cognitive performance prior to and/or following treatment, such as epilepsy, mood, and HRQoL were not systematically investigated across studies.

There is evidence to conclude that meningioma patients are faced with cognitive dysfunction in several cognitive domains before and (slightly less) after treatment. Clinicians should be aware of these deficits. Researchers should employ more rigorous methodologies. Better awareness, early diagnosis and treatment of cognitive deficits may improve outcome and quality of life in this patient population.

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CHAPTER 3

The first-time use of the computerized neuropsychological battery CNS Vital Signs in a Dutch neurological population

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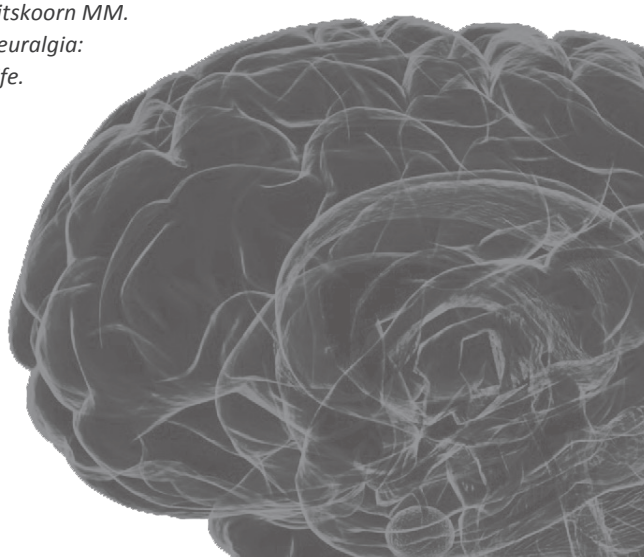

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INTRODUCTION

Cognitive impairments can often be found in patients with chronic pain disorders, in particular when attentional capacity, processing speed, or psychomotor speed are measured (1-3). These impairments have been shown to affect therapy adherence, personal relationships, daily functioning, capacity for work, leisure activities, mood, and quality of life (4, 5). Surprisingly, no prior studies have investigated cognitive functioning in patients with trigeminal neuralgia (TN). In particular, the subset of patients that are candidates for surgical microvascular decompression (MVD; a procedure that requires a craniotomy and frees the root of the trigeminal nerve from compression of an artery) seem at high risk for cognitive impairments, because of severe, long-standing and medically intractable pain.

In recent years various computerized neuropsychological test batteries such as the Central Nervous System Vital Signs (CNS VS) have been developed that offer an attractive alternative to (often more lengthy) traditional neuropsychological paper-based assessment.

In this study we evaluated the first-time use of the CNS VS battery as computerized clinical neuropsychological screening tool for cognitive dysfunction in patients with TN. The formal Dutch translation of CNS VS had not been used before in a Dutch neurological patient sample. A large group of patients with TN undergo neurosurgery in our hospital. Cognitive performance in these patients had not been studied before. We examined cognitive performance on these computerized tests in patients with TN before MVD in comparison with healthy controls.

PATIENTS AND METHODS

Patient population

Cases eligible for the current analyses were patients diagnosed with TN who were scheduled to undergo MVD between December 2010 and December 2012 at the Elisabeth-TweeSteden Hospital (Tilburg, the Netherlands). Exclusion criteria were: age under 18, history of intracranial neurosurgery, history of psychiatric or neurological disorders, history of cranial radiotherapy, lack of basic proficiency in Dutch and total unfamiliarity with the use of computers. Patients who were unable to undergo the neuropsychological test battery due to severe cognitive problems were additionally excluded.

Healthy controls

Patients were compared with data from 2 control groups of healthy subjects: a normative American control group (N = 1,069) from the CNS VS database (6), and a Dutch control group (N = 20) who was recruited from the general population.

CNS VS has a normative database from 1,069 subjects ranging in age from 7 to 90, drawn from the American population. In most age groups, there is a female predominance, ranging from 43% to 72%. Information about education of the American sample is not provided (6). Also no information was available from any of CNS VS' analyses regarding the establishment of the battery's normative data. It database comprises individuals who are in good health with no current or past psychiatric, neurologic, or cognitive disorder, and no current medication use.

To be included in our own control group, a subject had to be free of pain and sociodemographically comparable to the group of patients with TN. Participants were considered healthy if (a) there was no past or present psychiatric or neurologic disorder; (b) they had no other major medical illnesses in the past year prior to participation (e.g., cancer, myocard infarct); (c) they were free of use of any centrally acting psychotropic medication; and (d) did not have a history

of or current alcohol or drug abuse. Dutch healthy controls were group-wise matched during recruitment to the patient group according to age, gender, and educational level.

Procedure

One day before surgery, patients were hospitalized and tested. All patients were assessed with a standardized computerized neuropsychological test battery CNS VS (6). Test sessions were performed as part of the usual care in the Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands. Education was classified according to the coding system of Verhage ranging from 1 (only primary school) to 7 (university) (7). Patients also filled out the Dutch translation of the Hospital Anxiety and Depression Scale (HADS) (11). Socio-demographic information was collected by means of a checklist and interview. Clinical information was obtained from the electronic medical charts.

Dutch healthy controls were also assessed with CNS VS. The computerized neuropsychological tests were, depending on participants' preference, administered individually at Tilburg University (Tilburg, The Netherlands), Elisabeth-TweeSteden Hospital (Tilburg, The Netherlands), or at participants' homes. Well-trained test technicians ensured appropriate conditions and remained present during the entire assessment. Participants filled out a questionnaire on health status.

Instruments

Cognitive functioning was assessed with the CNS VS battery, which consists of 7 tests (Table 1) (6). The pencil and paper versions on which these tests are based are widely used by neuropsychologists. CNS VS has a normative database from 1,069 normal subjects ranging from age 8 to 90, drawn from the American population. Testing results are presented in subject (raw) scores, age-matched standard scores, and percentile ranks. CNS VS standard scores have a mean of 100 and a standard deviation of 15; higher scores indicate better performance. CNS VS has an official Dutch translation. The time needed to complete the battery is short, approximately 30–40 min (6). For the purpose of this study, patients were evaluated on 5 cognitive domains (composite memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility). We refer to complex attention and cognitive flexibility as measures of executive functioning. For a detailed description of the calculations of the domain scores, we suggest visiting the link http://www.cnsvs.com.

Anxiety and depression were assessed with a Dutch translation of the Hospital Anxiety and Depression Scale (HADS) (11). This self-report screening instrument consists of 14-items: each subscale (i.e., anxiety and depression) includes 7 items with response options ranging from 0-3, resulting in a score from 0-21 for each subscale, with higher scores representing more anxiety and depression symptoms.

Table 1 CNS Vital Signs description of clinical domains and tests (6)

Domains	Tests	Description
Memory	Verbal memory test	Learning a list of 15 words, with an immediate recognition, and after 6 more tests a delayed recognition trial
	Visual memory test	Learning a list of 15 geometric figures, with an immediate recognition, and after 5 more tests a delayed recognition trial
Psychomotor speed	Finger tapping	Pressing the space bar with the right and left index finger as many times in 10 seconds
	Symbol digit coding	Above-mentioned
Reaction time	Stroop test	In the first part, pressing the space bar as soon as the words RED, YELLOW, BLUE, and GREEN appear In the second part, pressing the space bar as soon as the color of the word matches what the word says In the third part, pressing the space bar as soon as the word does not match what the word says
Complex attention	Continuous performance test	Responding to a target stimulus "B" but no any other letter
	Shifting attention task	Above-mentioned
	Stroop test	Above-mentioned
Cognitive flexibility	Shifting attention task	Above-mentioned
	Stroop test	Above-mentioned

Statistical analyses

Since no information was available from any of CNS VS' analyses regarding the establishment of the battery's normative data, standard scores (i.e., scores normalized and corrected for age by CNS VS) were used in the comparative analyses between the American sample and patients with TN. Raw scores were used in the comparative analyses between the Dutch sample and patients with TN.

We performed several one-sample T-tests to explore whether TN patients differed from the normative sample (N = 1,069; *M* = 100, *SD* = 15 (6)) in cognitive test performance. To determine whether there was a differences in test performance between patients and the Dutch sample (N = 20), several independent-samples T-tests were used.

In addition, to gain insight in individual test performances, the number of patients scoring 1.5 *SD* below average was counted for each of the 5 cognitive domains.

A series of Pearson product-moment correlation coefficients was calculated to examine the potential relationship of anxiety and depression with cognitive performance.

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 24.0.

RESULTS

Demographic and clinical characteristics

Of the 43 patients scheduled for MVD, 11 patients were excluded from participation: 2 patients had a current neurological and psychiatric disorder, respectively multiple sclerosis (MS) and depression; 8 patients had previous MVD. In addition, 1 patient was excluded from further analysis because the test was interrupted due to severe facial pain. The final patient group consisted of 32

eligible patients (14 females, 18 males, M age = 54, age range: 24-74). The Dutch sample comprised 20 healthy subjects (11 females, 9 males, M age = 50, age range: 22-80 years). The patients and healthy controls were comparable with respect to age, gender and educational level (Table 2).

Table 2 Demographic and clinical characteristics

Characteristics	Patients (N = 32)	Healthy controls (N = 20)	T-test, χ^2-test or Fisher's Exact test	*p*
Age (mean ± *SD*)	54.00 ± 12.26	49.60 ± 14.86	t = 1.17	.25
Male/Female (n/n)	18/14	9/11	χ^2 = .26	.61
Highest level of education (mean; range) [a]	2.97 (1-7)	3.10 (1-7)	Fisher's Exact test	.86
Use of AEDs, n (%) [b]	26 (81.25)	NA		
Anxiety pre-operatively mean (*SD*)	5.71 ± 3.16 [c]	NA		
Depression pre-operatively mean (*SD*)	4.72 ± 3.19 [d]	NA		

[a] Education was classified according to the coding system of Verhage ranging from 1 (only primary school) to 7 (university) (7)
[b] Data on use of AEDs was available in 30 of the 32 patients due to missing reports
[c] Data on pre-operative levels of anxiety and depression was available in 28 of the 32 patients
[d] Data on post-operative levels of anxiety and depression was available in 28 of the 32 patients
NA = not applicable
* $p < .05$

Test performance of TN patients in comparison with the American normative sample

Significant differences were found in mean standard scores between patients and the American normative sample on measures of composite memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility, with patients performing worse than CNS VS' normative sample (Table 3).

Table 3 Comparison of means of the patient group (N = 32) compared with the normative sample

Variables	Mean ± *SD* [a]	T-test	*p*
Composite memory	88.66 ± 14.71	-4.36	<.001*
Psychomotor speed	83.72 ± 21.61	-4.26	<.001*
Reaction time	92.47 ± 17.18	-2.48	.019*
Complex attention	84.72 ± 26.72	-3.24	.003*
Cognitive flexibility	86.72 ± 26.15	-2.87	.007*

[a] CNS VS standard scores have a mean of 100 and a standard deviation of 15; higher scores indicate better performance
* $p < .05$

Test performance of TN patients in comparison with the Dutch sample

Significant differences were found in mean raw scores between patients and the Dutch sample on measures of composite memory, psychomotor speed, complex attention, and cognitive flexibility, with patients performing worse than the Dutch control group. No significant differences were found in mean raw scores between the groups on reaction time (Table 4).

Table 4 Comparison of means of the patient group (N = 32) compared with the Dutch sample (N = 20)

Variables	Patients Mean ± *SD* [a]	Dutch sample Mean ± *SD* [a]	T-test	*p*
Composite memory ˆ	90.78 ± 7.36	95.80 ± 8.45	-2.26	.028*
Psychomotor speed ˆ	141.53 ± 32.01	165.10 ± 35.90	-2.46	.017*
Reaction time ˇ	719.09 ± 135.68	667.30 ± 147.70	1.30	.201
Complex attention ˇ	13.78 ± 11.84	6.80 ± 5.28	2.90	.006*
Cognitive flexibility ˆ	30.13 ± 25.24	44.85 ± 15.16	-2.63	.011*

[a] Raw scores; ˆ higher score = better performance; ˇ lower score = better performance
* $p < .05$

Individual test performance of patients with TN

We found that 35% (highest proportion) of our patients had deficits on psychomotor speed, 32% on reaction time, 25% on complex attention and cognitive flexibility, and 19% on composite memory and processing speed (data not shown).

Anxiety and depression

With regard to anxiety and depression scores there was no significant correlation with any of the cognitive domains ($p > .05$; data not shown).

DISCUSSION

In this study we evaluated the first-time use of the formal Dutch translation of the CNS VS battery as computerized clinical neuropsychological screening tool for cognitive function in a (Dutch) neurological patient population. This was the first study on cognitive function in patients with TN. Cognitive dysfunction was examined with CNS VS before MVD and compared to healthy controls. For the purpose of this study we compared patients' cognitive performance with performance of 2 control groups of healthy subjects: the normative American data from the CNS VS database and a group of Dutch healthy individuals that we recruited ourselves.

In line with previous data of patients with other chronic pain conditions, we observed impairments in composite memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility. Patients with TN performed significantly worse in comparison with the American normative sample on all of the 5 selected cognitive functions. Comparisons of patients with TN with our Dutch control group of healthy subjects revealed quite the same pattern of differences in mean test performance (i.e., composite memory, psychomotor speed, complex attention, and cognitive flexibility), with the exception of reaction time where no mean group difference was found. These results suggest that the American norms of the CNS VS database are applicable to our group of Dutch patients. Previous findings showed impaired executive function in chronic pain syndromes, which suggested that the frontal brain regions that control executive function may be the same as those involved in pain processing (9 - 11). In our study we also found deficits in the domains of memory, psychomotor speed, and reaction time.

Evaluation of individual test performances, showed that 35% (highest proportion) of our patients had deficits on psychomotor speed, 32% on reaction time, 25% on complex attention and cognitive flexibility, and 19% on composite memory and processing speed. These results indicate that cognitive deficits can be objectified by CNS VS and that substantive proportions of patients with TN have cognitive deficits.

The present study is the first study that explored cognitive functioning with the computerized neuropsychological test battery (i.e., CNS VS) in Dutch patients who suffer from TN. However, this study has a few limitations. Firstly, the size of the patient sample in this study is small. Therefore, the results should be interpreted with caution and findings should be replicated in larger patient samples to compare the results. A second limitation is that our data concern a specific group of patients that was cognitively tested one day before MVD. Waiting for surgery is often accompanied with high levels of anxiety, which are known to affect cognitive functioning negatively (12, 13, 14). However, there was no statistically significant correlation between pre-operative anxiety and pre-operative cognitive functioning. A third limitation is that the results are possibly confounded by the fact that the majority of TN patients were on anti-convulsant medication or opioids. It is well known that these drugs can interfere with cognitive functions (15-18). We are therefore unable to answer the question as to what the precise cause or causes of cognitive impairments in TN patients is or are. Clearly, follow-up research is needed to study the possible contribution of drug side effects.

Despite these methodological limitations, we can conclude that TN patients are at risk for cognitive deficits, and that clinicians should be aware of this risk and the subsequent negative impact on socioprofessional life. As mild or moderate cognitive impairments may not be detected with routine medical examinations, we propose that TN patients are routinely evaluated with neuropsychological testing (19). For this purpose, a brief computerized neuropsychological screening instrument can be a practical alternative to traditional neuropsychological testing that takes several hours. As MVD generally provides pain relief in many TN patients, and medication can frequently be tapered off after surgery, we hypothesize that MVD is a means to improve cognitive impairments. Future studies will help to better define the impact of other (psychological and clinical) variables that are associated with neuropsychological functioning in patients suffering from TN.

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CHAPTER 4

Cognitive improvement in meningioma patients after surgery: clinical relevance of computerized testing

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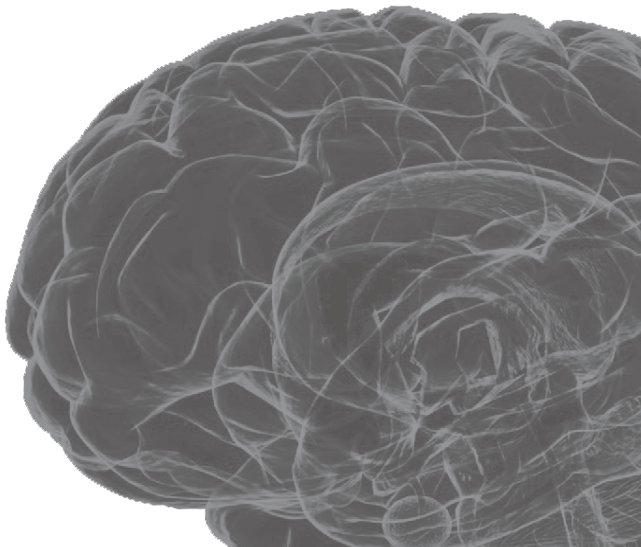

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INTRODUCTION

Cognitive dysfunction is common in patients with a primary tumor (1). Most studies have focused on glioma patients. However, less is known about cognitive functioning in meningioma patients and the impact of surgical treatment (2-9). In most of the studies that did focus on meningioma patients, cognitive functioning was not systematically assessed pre-operatively (4, 7, 8). In 2003 Tucha and colleagues examined 54 patients with frontal meningiomas before and after surgery(3). They found that in comparison with healthy controls, meningioma patients showed significant pre-operative impairments on working memory, fluency functions, tonic alertness, processing speed, shifting, divided attention, and flexibility. Post-operatively, patients' scores were again lower than the scores of healthy controls, although an improvement of attentional functions and no deterioration of overall cognitive functioning was observed.

This is the first study in which meningioma patients were tested with a brief computerized neuropsychological test battery (i.e., CNS Vital Signs) that provides a rapid, efficient and cost-effective screen for cognitive dysfunction (10). In this prospective follow-up study we examined the incidence and severity of cognitive dysfunction in meningioma patients before and 3 months after surgery, both at group level and individual patient level. We also evaluated possible changes in cognitive function after surgery. In addition, we examined status of cognitive functioning for different tumor locations and associations between tumor location and cognitive improvement over time, and evaluated anxiety and depression pre- and post-operatively.

PATIENTS AND METHODS

Patient population

The present study was part of a larger study in which neurosurgical patients, admitted for brain surgery at the Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands, are neuropsychologically assessed pre- and post-operatively. Cases eligible for the current analyses were patients diagnosed with a single meningioma who were treated with surgery between November 2010 and June 2013. Most of these patients had a meningioma with a diameter > 3 cm, as we tend to adopt a wait-and-scan approach in patients with a smaller meningioma or treat them with Gamma Knife radiosurgery. Exclusion criteria were: age under 18, history of intracranial neurosurgery, history of psychiatric or neurological disorders, history of cranial radiotherapy, lack of basic proficiency in Dutch and total unfamiliarity with the use of computers. Patients who were unable to undergo the neuropsychological test battery due to severe cognitive problems were additionally excluded.

Procedure

The study was set up as a prospective follow-up design. One day before surgery, patients were hospitalized and tested. Post-operative assessment took place 3 months after surgery at neurosurgical follow-up. All patients were assessed with a standardized computerized neuropsychological test battery, CNS Vital Signs (CNS VS) (10). Test sessions were performed as part of the usual care in the Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands. Patients also filled out the Dutch translation of the Hospital Anxiety and Depression Scale (HADS) at both time-points (11). Results on the tests and questionnaires were evaluated in a multidisciplinary group (including a nurse, a neuropsychologist, and a rehabilitation physician) at 3 months after surgery. Socio-demographic information was collected by means of a checklist and interview. Clinical information was obtained from the electronic medical charts.

The study was approved by the Medical Ethics Committee Brabant, The Netherlands (File number: NL41351.008.12).

Instruments

Cognitive functioning was assessed by a computerized neuropsychological screening instrument, CNS VS, which consists of 7 tests (Table 1) (10). The pencil and paper versions of these tests are widely used by neuropsychologists. CNS VS has a normative database from 1,069 subjects ranging in age from 7 to 90, drawn from the American population. Testing results are presented in subject (raw) scores, age-matched standard scores, and percentile ranks. CNS VS standard scores have a mean of 100 and a standard deviation of 15; higher scores indicate better performance. The tests are assumed to be suitable for repeated testing because of the random presentation of stimuli, thereby minimizing practice effects. CNS VS has an official Dutch translation. The time needed to complete the battery is short, approximately 30–40 min (10).

Depression and anxiety were assessed with a Dutch translation of the HADS (11). The HADS is a 14-item self report screening scale which contains 7-item scales: 1 for anxiety and 1 for depression; both with a score range of 0–21. The HADS is considered to be unbiased by coexisting general medical conditions (12). The HADS has been validated in a Dutch sample (13).

Table 1 CNS Vital Signs description of clinical domains and tests (10)

Domains	Tests	Description
Memory	Verbal memory test	Learning a list of 15 words, with an immediate recognition, and after 6 more tests a delayed recognition trial
	Visual memory test	Learning a list of 15 geometric figures, with an immediate recognition, and after 5 more tests a delayed recognition trial
Processing speed	Symbol digit coding	Corresponding numbers and symbols
Executive functioning	Shifting attention task	Shifting from one instruction set to another quickly and accurately (matching geometric objects either by shape or by color)
Psychomotor speed	Finger tapping	Pressing the space bar with the right and left index finger as many times in 10 seconds
	Symbol digit coding	Above-mentioned
Reaction time	Stroop test	In the first part, pressing the space bar as soon as the words RED, YELLOW, BLUE, and GREEN appear In the second part, pressing the space bar as soon as the color of the word matches what the word says In the third part, pressing the space bar as soon as the word does not match what the word says
Complex attention	Continuous performance test	Responding to a target stimulus “B” but no any other letter
	Shifting attention task	Above-mentioned
	Stroop test	Above-mentioned
Cognitive flexibility	Shifting attention task	Above-mentioned
	Stroop test	Above-mentioned

STATISTICAL ANALYSIS

Standard scores (i.e., scores normalized and corrected for age by CNS VS) were used in all analyses. We performed several one-tailed independent one-sample T-tests to explore whether meningioma patients differed from healthy controls (American normative database, *M* = 100, *SD* = 15 (10)) in cognitive functioning before and after surgery. To explore whether cognitive functions changed over time, two-tailed paired-samples T-tests were conducted. Effect sizes were calculated to determine the magnitude of the difference between patients and healthy controls and the change over time.

To gain insight in individual test performances, the number of patients scoring 'low' or 'very low' (i.e., 1.5 and 2 *SD* below average) was counted. These scores are indicated by CNS VS as 'moderate deficit and impairment possible or low' and 'deficit and impairment likely or very low'. The McNemar's test of symmetry was used to compare the proportions of patients scoring low or very low before and after surgery. Cases of individual changes in severity (i.e., very low, low, low average, average, above average) of cognitive functioning from pre-test to post-test was calculated.

To explore whether there was a difference in status of cognitive functioning for different tumor locations, two-tailed independent-samples T-tests were performed. Associations between tumor location and cognitive improvement over time were explored with Fisher's exact tests.

Paired-samples T-tests were performed to explore whether there was a difference in anxiety and depression before and after surgery. A series of Pearson product-moment correlation coefficients was calculated to examine the strength of the relationship of anxiety and depression with cognitive performance.

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 24.0.

RESULTS

Demographic and clinical characteristics

Figure 1 shows the flow diagram for the study. Table 2 shows patients' demographic and clinical characteristics. Mean age before surgery was 55 years and there was a female prominence (68%), which is similar to the normative database of CNS VS consisting of more women than men (ranging from 58 to 66%).

Test performance of meningioma patients at group level pre- and post-operatively

Meningioma patients showed significantly lower scores on all (7) cognitive domains both pre-operatively and post-operatively, in comparison with the normative healthy American control group ($p < .05$) (Table 3).

On the pre-operative assessment, medium effect sizes were found for psychomotor speed and reaction time. Medium (to large) effect sizes were found for memory, processing speed, and executive functioning. A medium to large effect was found for complex attention and cognitive flexibility. On the post-operative assessment, most of the effect sizes were small to medium, with the exception of psychomotor speed where a small effect size was found.

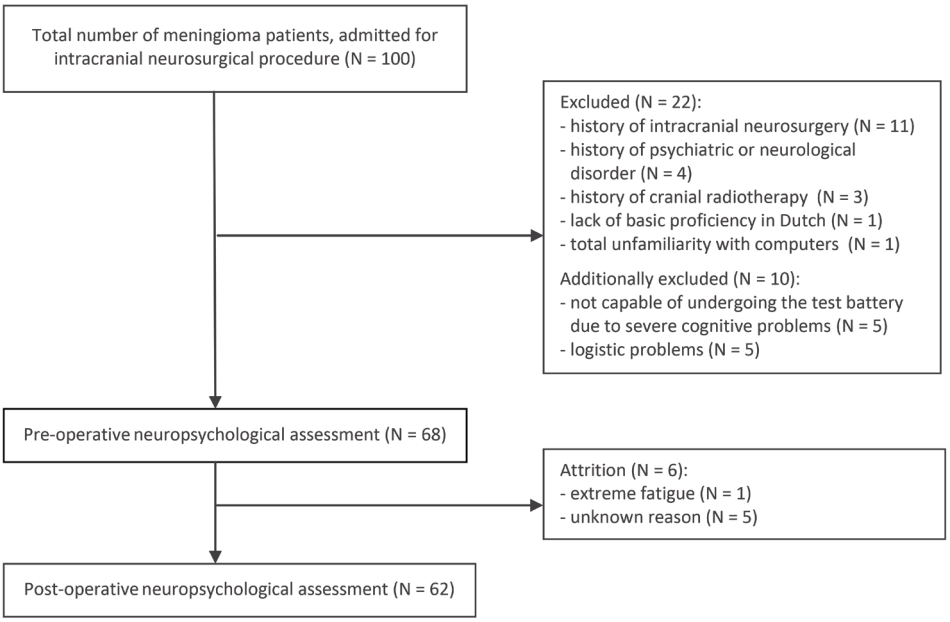
The two-tailed within-subjects analyses showed a significant change over time on 5 out of 7 domains ($p < .05$) (Table 3). We observed significant improvements in the mean standardized domain scores on 5 out of 7 domains: memory, complex attention, cognitive flexibility, processing speed, and executive functioning. The effect sizes of change were small.

Table 2 Demographic and clinical characteristics

Characteristics	
Female (N (%))	46 (67.6)
Age (mean; range)	55.66; 36-74
Handedness (rt/lt)	60/8
Education (mode; range) [a]	4.90; 4-7
Localization tumor	
Hemisphere	
Left (N (%))	30 (44.1)
Right (N (%))	33 (48.5)
Bilateral (N (%))	5 (7.4)
Lobe	
Frontal	38
Temporal	8
Parietal	5
Occipital	2
Frontalparietal	2
Frontaltemporal	2
Parietaloccipital	1
Fossa posterior	9
NA	1
Tumor grade (WHO)	
I	63
II	5
III	0
Maximum tumor diameter (cm^3; range)	4.38; 1.7 - 8 [b]
Epilepsy (N (%))	16 (23.5)
Use of AEDs (N (%))	14 (21.9) [c]
Radiotherapy within 3 months (N (%))	1 (1.47)
Anxiety and depression (HADS)	
Anxiety pre-operatively mean (*SD*)	6.73 ± 4.16 [d]
Depression pre-operatively mean (*SD*)	5.88 ± 4.22 [d]
Anxiety post-operatively mean (*SD*)	5.08 ± 4.10 [e]
Depression post-operatively mean (*SD*)	3.73 ± 3.12 [e]

[a] Education was classified according to the coding system of Verhage ranging from 1 (only primary school) to 7 (university) (14)
[b] Data on volume of mass lesions was available in 67 of the 68 patients
[c] Data on use of AEDs was available in 64 of the 68 patients due to missing reports
[d] Data on pre-operative levels of anxiety and depression was available in 60 of the 68 patients
[e] Data on post-operative levels of anxiety and depression was available in 52 of the 68 patients
NA = not applicable

Figure 1 Flow of patients



Individual test performances of meningioma patients pre- and post-operatively

Individual patients that scored lower than 1.5 *SD* below average ('low' or 'very low' scores) were counted for each cognitive domain. Pre-operatively, 47 out of 68 patients (69%) scored low or very low in 1 or more cognitive domains. Thirteen out of 68 patients (19%) had deficits (low or very low scores) in more than 4 domains. In general, 43% of the patients (highest proportion) showed deficits on cognitive flexibility, followed by 41 and 37% of the patients with impairments on executive functioning and complex attention respectively.

Post-operatively, 27 out of 62 patients (44%) scored low or very low in 1 or more cognitive domains. Eight out of 62 patients (13%) had deficits on more than 4 domains. In general, the highest proportion of patients (26%) showed deficits on processing speed, followed by cognitive flexibility and reaction time (both 23%). According to the McNemar's test of symmetry, there was a significant difference in the proportion of patients scoring low or very low on 1 or more domains pre- and post-operatively ($p < .05$). The test provides strong evidence of an improvement of cognitive functioning after surgery.

In addition, we determined the change in severity (i.e., very low, low, low average, average, above average) of cognitive functioning from pre-test to post-test (see Fig. 2). For all domains, most of the patients starting from the category 'very low' and 'low' made a positive change to categories of better cognitive performance after surgery. In particular, this positive change was most frequent for memory i.e., 21% of the patients improved 2 or more categories. For cognitive flexibility and executive functioning, 19 % of the patients improved 2 or more categories, followed by complex attention (18%), psychomotor speed (15%), reaction time (11%), and processing speed (10%). For all domains, the patients who scored 'above average' on the pre-test did not fall back to lower categories after surgery, with the exception of 1 patient who changed from 'above average'

to 'very low' on the domain reaction time. We could not find an explanation for this extreme decline in this patient.

Table 3 Comparison of means of the patient group at group level pre- and post-operatively

Variable	Mean (*SD*) [a]	Mean difference	T-test	*p*	Effect size d [b]
Pre-operative assessment					
Memory	86.63 (19.15)	-13.37	-5.76	<.001*[c]	.78
Psychomotor speed	90.31 (22.82)	-9.69	-3.50	.001*	.50
Reaction time	89.91 (19.28)	-10.09	-4.32	<.001*	.58
Complex attention	82.03 (27.86)	-17.97	-5.32	<.001*	.80
Cognitive flexibility	82.34 (27.26)	-17.66	-5.34	<.001*	.80
Processing speed	88.29 (17.85)	-11.71	-5.41	<.001*	.71
Executive functioning	84.40 (24.06)	-15.60	-5.35	<.001*	.78
Post-operative assessment					
Memory	93.90 (17.64)	-6.10	-2.72	.004*[d]	.37
Psychomotor speed	95.34 (20.35)	-4.66	-1.80	.038*	.26
Reaction time	92.74 (21.20)	-7.26	-2.70	.005*	.40
Complex attention	90.77 (23.05)	-9.23	-3.15	.002*	.47
Cognitive flexibility	92.44 (22.60)	-7.57	-2.64	.006*	.39
Processing speed	93.55 (18.37)	-6.45	-2.77	.004*	.38
Executive functioning	93.94 (21.65)	-6.07	-2.21	.016*	.33
Pairs					
1 - Memory	86.76 (19.07) 93.90 (17.64)	-7.14	-3.221	.002*	.39
2 - Psychomotor speed	90.61 (23.30) 95.34 (20.35)	-4.73	-1.757	.084	.22
3 - Reaction time	90.73 (19.14) 92.74 (21.20)	-2.01	-.768	.446	.10
4 - Complex attention	83.53 (28.28) 90.77 (23.05)	-7.24	-2.079	.042*	.28
5 - Cognitive flexibility	84.24 (27.57) 92.44 (22.60)	-8.20	-2.518	.014*	.33
6 - Processing speed	89.42 (17.88) 93.55 (18.37)	-4.13	-2.652	.010*	.23
7 - Executive functioning	86.44 (23.95) 93.94 (21.65)	-7.50	-2.648	.010*	.33

Note: N pretest = 68, N posttest = 62

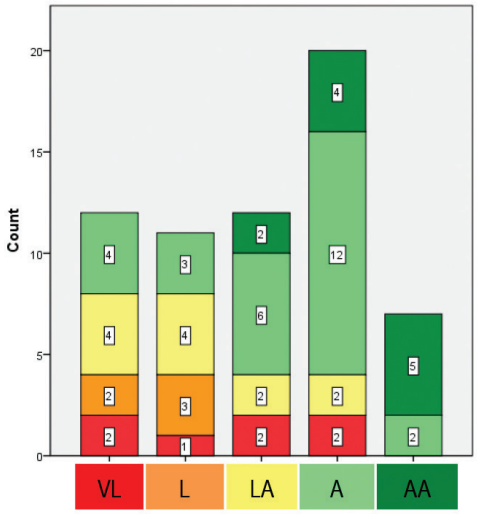
[a] CNS VS standard scores have a mean of 100 and a standard deviation of 15; higher scores indicate better performance

[b] Cohen's *d* effect sizes: ≤ .20 -.30: small, .50: medium, ≥. 80: large (15)

[c] one-tailed

[d] two-tailed

Memory:



Psychomotor speed:

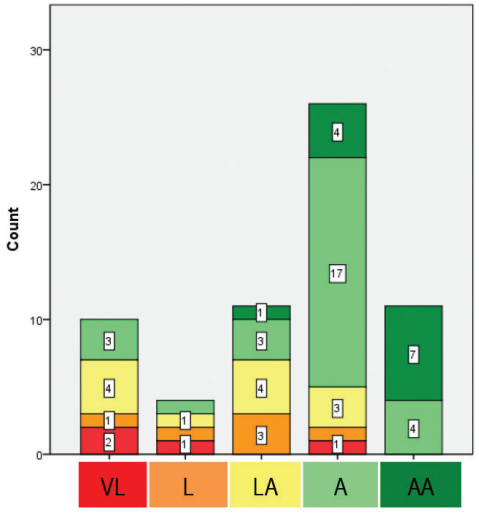
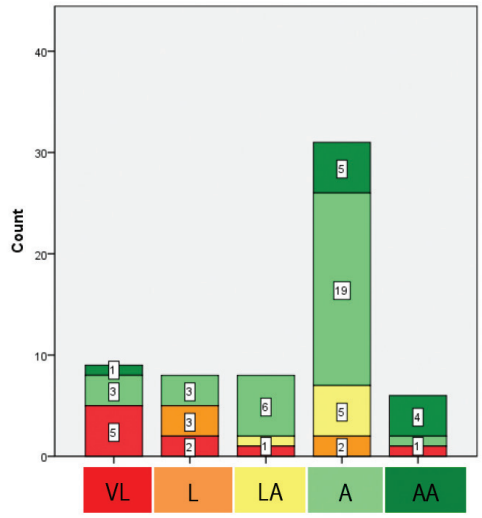


Figure 2 Cognitive functioning from pre-test to post-test
The X-axis represents the patients scoring very low, low, low average, average, and above average on a domain pre-operatively (pre-op). The coloured blocks represent the number of patients post-operatively (post-op) in each category (i.e., different colours). For example for memory, pre-operatively 12 patients scored very low in the domain (total of all coloured blocks at very low), of whom post-operatively 2 patients kept a very low domain score, 2 had a low score, 4 improved to low average and 4 to an average domain score.

Reaction time:



Complex attention:

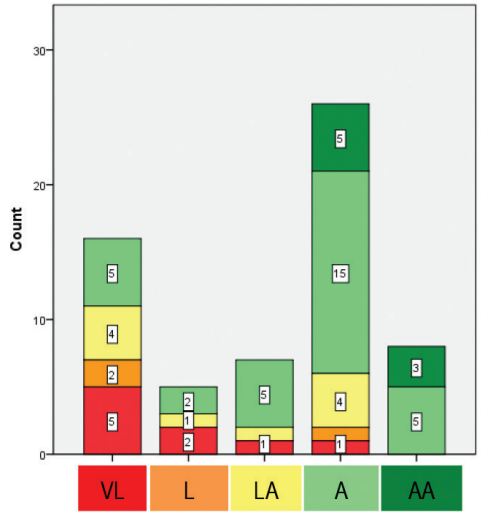
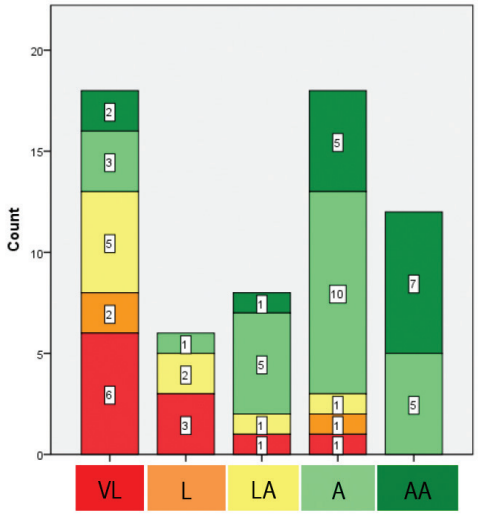


Figure 2 Continued
The X-axis represents the patients scoring very low, low, low average, average, and above average on a domain pre-operatively (pre-op). The coloured blocks represent the number of patients post-operatively (post-op) in each category (i.e., different colours). For example for memory, pre-operatively 12 patients scored very low in the domain (total of all coloured blocks at very low), of whom post-operatively 2 patients kept a very low domain score, 2 had a low score, 4 improved to low average and 4 to an average domain score.

Cognitive flexibility:



Processing speed:

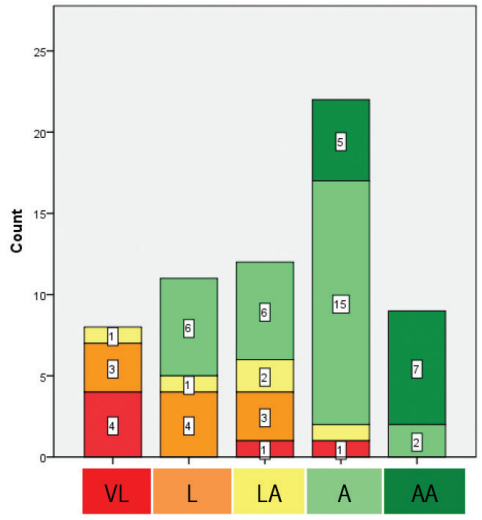


Figure 2 Continued
The X-axis represents the patients scoring very low, low, low average, average, and above average on a domain pre-operatively (pre-op). The coloured blocks represent the number of patients post-operatively (post-op) in each category (i.e., different colours). For example for memory, pre-operatively 12 patients scored very low in the domain (total of all coloured blocks at very low), of whom post-operatively 2 patients kept a very low domain score, 2 had a low score, 4 improved to low average and 4 to an average domain score.

Executive functioning:

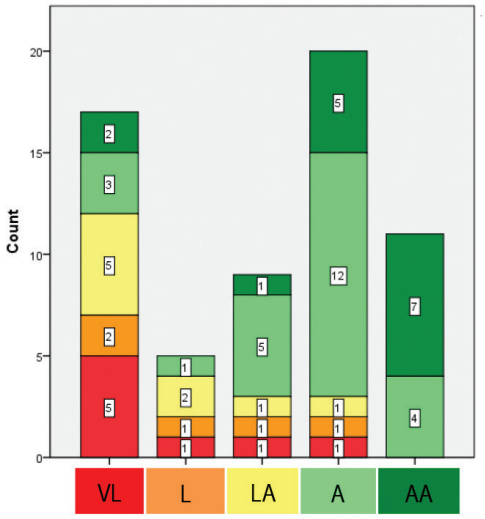


Figure 2 Continued
The X-axis represents the patients scoring very low, low, low average, average, and above average on a domain pre-operatively (pre-op). The coloured blocks represent the number of patients post-operatively (post-op) in each category (i.e., different colours). For example for memory, pre-operatively 12 patients scored very low in the domain (total of all coloured blocks at very low), of whom post-operatively 2 patients kept a very low domain score, 2 had a low score, 4 improved to low average and 4 to an average domain score.

Tumor location and pre-and post-operative cognitive functioning

With respect to cognitive functioning and tumor location, no significant differences in pre-operative cognitive functioning were found between supratentorial and infratentorial tumors, between skull base and convexity tumors, and between skull base and convexity/falx tumors. Neither were there significant differences in pre-operative cognitive functioning between tumors located in the left or right hemisphere (all *p*'s > .05). In addition, no significant differences in post-operative cognitive functioning were found between the tumor location groups, except for the domain of complex attention where a significant difference was found between supratentorial and infratentorial tumors, with better performance of the latter group ($p < .05$).

No significant associations were found between tumor location and cognitive improvement over time ($p > .05$). The proportion of patients who showed improvement in cognitive functioning following surgery was equal in patients with skull base tumors, convexity tumors and convexity/falx tumors. No significant changes in cognitive functioning were found between left sided and right sided tumors, neither between supratentorial and infratentorial tumors ($p > .05$).

Pre- and post-operative anxiety and depression

In general, on the pre-operative assessment 40 and 37% of the patients scored above the cut-off (≥ 8) for anxiety and depression, respectively. On the post-operative assessment, 33 and 10% of the patients scored above cut-off values on the anxiety and depression scales, respectively. On the pre-operative assessment, anxiety score was not significantly correlated with any of the cognitive domains ($p > .05$). Depression score significantly correlated negatively with psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, and executive functioning (r ranging from -.29 to -.40). Following surgery there was a significant reduction in the levels of both anxiety and depression symptoms ($p < .05$). On the post-operative assessment, anxiety correlated negatively with complex attention (r = -.30). Depression was negatively correlated with memory and complex attention (r = -.28 and r = -.36).

DISCUSSION

This is the first prospective study that thoroughly investigated the incidence and severity of cognitive dysfunction of meningioma patients before and 3 months after surgery, and the change of cognitive dysfunction over time, both at group level and individual patient level.

Our findings indicate that the majority of meningioma patients already have mild to moderate cognitive deficits before surgery. They are faced with cognitive dysfunction in all cognitive domains tested: memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, and executive functioning. Significant differences of medium to large effect size were found between our patients and the normative control group. Three months after surgery, test performance on 5 out of 7 domains (i.e., memory, complex attention, cognitive flexibility, processing speed, and executive functioning) improved significantly. For psychomotor speed and reaction time, no significant improvement was observed. In fact, psychomotor speed and reaction time were less impaired than other cognitive domains at baseline, which may have left less room for improvement. Although clear conclusions can be drawn about the existence of cognitive deficits in patients with meningioma, it must be noted that the observed deficits are of mild to moderate severity.

At the individual level, we found that pre-operatively, 47 out of 68 patients (69%) scored low or very low on 1 or more cognitive domains. Post-operatively, 27 out of 62 patients (44%) scored low or very low on 1 or more cognitive domains. Only a small proportion of the patients had cognitive deficits in more than 4 domains (i.e., 19% of the patients on the pre-operative assessment, and 13% of the patients on post-operative assessment). Most of the patients starting from the category ‘very low’ and ‘low’ made a positive change to categories of better cognitive performance after surgery. This positive change was most frequent for memory (21% of the patients changed ≥ 2 categories) and least frequent for processing speed (10% of the patients changed ≥ 2 categories). On average, surgery improves cognitive functioning, but still leaves a large proportion of meningioma patients with cognitive deficits 3 months after surgery. We are currently adding a 12-month follow-up to the design of our study to investigate possible further improvement over time and to identify the predictors of cognitive improvement in meningioma patients after surgery.

Our study demonstrates in addition that a brief computerized neuropsychological test battery is able to identify similar cognitive deficits as found in the study of Tucha et al. (3). Thus, a computerized test battery seems an adequate and time-efficient clinical instrument to detect cognitive impairments in meningioma patients.

It may be suggested that low(er) pre-operative cognitive functioning on the day before surgery may be explained by high anxiety. However, there was no statistically significant correlation between pre-operative anxiety and pre-operative cognitive functioning, which makes this explanation unlikely. On the other hand, there was an association of pre-operative depression with cognitive function. Future research will help to better define the influence of preexisting depression with cognitive dysfunction after surgery. In general, on the pre-operative assessment most of the patients (60 and 63%) scored below the cut-off (≤ 8) for anxiety and depression respectively. On the post-operative assessment, there was a significant reduction of both anxiety and depression symptoms (i.e., 77 and 90% of the patients scored below the cut-off for anxiety and depression respectively).

A Dutch control group was not available. We compared the standard scores of the patients on 7 cognitive domains with the normative healthy American control group from CNS VS. In an earlier study we found that the performance on CNS VS tests of the Dutch control group of healthy participants was comparable to the American control group (14). Therefore, we consider it unlikely that the interpretations of the results of our Dutch meningioma group are flawed by comparison with an American control group.

CNS VS as an instrument has a few shortcomings. CNS VS is assumed to be suitable for repeated testing because of the random presentation of stimuli (10). Despite the chance that a patient exactly gets the same stimuli twice is negligible, there still could be a learning effect of the battery in general: the patient knows what to expect the second time. This phenomenon is also known as test-wiseness, which means that a test-taking strategy can be taught by instruction and that the knowledge gained will enable a test-wise examinee to obtain a higher score than an equally knowledgeable examinee who lacks test sophistication (14). However, we included a Dutch control group (N = 20) in addition to the American control group in our study on cognitive deficits in patients with trigeminal neuralgia with the aid of CNS VS (14) and found no effects of repeated testing.

We are aware that for some patients computerized testing is more stressful than for others, for example for older patients who are not familiar with computers (18). Iverson and colleagues (19) found that people with 'frequent' computer use performed better than people with 'some' computer use on tests requiring rapid visual scanning and keyboard work. In our study, we have noticed that when patients are too slow, they cannot follow the test correctly and have lower scores in all cognitive domains (memory, executive functioning etc.). We excluded patients with total unfamiliarity with computers. Neuropsychological technicians of computerized neuropsychological tasks should therefore be aware of the difference that may exist between patients with low versus high frequent computer familiarity.

In this study most of the patients had a meningioma with a diameter > 3 cm. All patients were selected for surgical treatment. With regard to smaller meningiomas we tend to adopt a wait-and-scan approach or treat them with Gamma Knife radiosurgery. Performance in our group of surgically treated patients may be slightly worse than performance in the whole population of meningioma patients probably due to symptomatic mass effect. Therefore, it is difficult to compare and generalize the results of this study to patients with smaller meningiomas.

Five patients were excluded due to severe cognitive problems because they were not capable of undergoing assessment with CNS VS. As a result, the incidence and severity rates of cognitive dysfunction may be an underestimation in this patient group.

We did not find significant differences in pre-operative and post-operative cognitive functioning based on tumor localization, except for the domain of complex attention where post-

operative performance was better for patients with infratentorial tumors. In line with Tucha and colleagues, we did not find significant differences between left sided and right sided tumors in either the pre- or post-operative assessment (3). On the other hand, Dijkstra and colleagues found that left sided as opposed to right sided tumors were more related to verbal deficits after treatment (4). The lack of effect of laterality in cognitive results between left sided and right sided hemisphere meningioma tumors could be explained by the fact that CNS VS has a smaller verbal emphasis than other neuropsychological batteries often have. No significant associations were found between tumor location and cognitive improvement over time. In a follow-up study we will investigate predictors of cognitive functioning in a larger group of meningioma patients.

We did not investigate other variables that are associated with neuropsychological functioning in meningioma patients. For example, epilepsy, anti-epileptic drugs, and other psychological factors may negatively affect neurocognitive functioning in meningioma patients (4, 5). Specification of predictors on cognitive functioning was beyond the scope of this study that merely aimed to report on incidence and severity.

CONCLUSION

We conclude that meningioma patients are faced with cognitive dysfunction in several cognitive domains both pre- and 3 months post-operatively. After surgery, cognitive functioning improved in a large proportion of patients, although most cognitive deficits are of mild to moderate severity. Our study also demonstrates that a rapid, efficient and cost-effective computerized neuropsychological test battery is a good alternative for conventional, time-consuming neuropsychological testing.

Based on the results of this study, clinicians and patients can be better informed about cognitive dysfunction in meningioma patients. We expect that diagnosis and treatment of these cognitive deficits will improve outcomes and quality of life in meningioma patients by providing appropriate care (for example cognitive rehabilitation (20)), adjusted to the cognitive profile of the individual patient.

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CHAPTER 5

Evaluation of normative data of a widely used computerized neuropsychological battery: applicability and effects of sociodemographic variables in a Dutch sample

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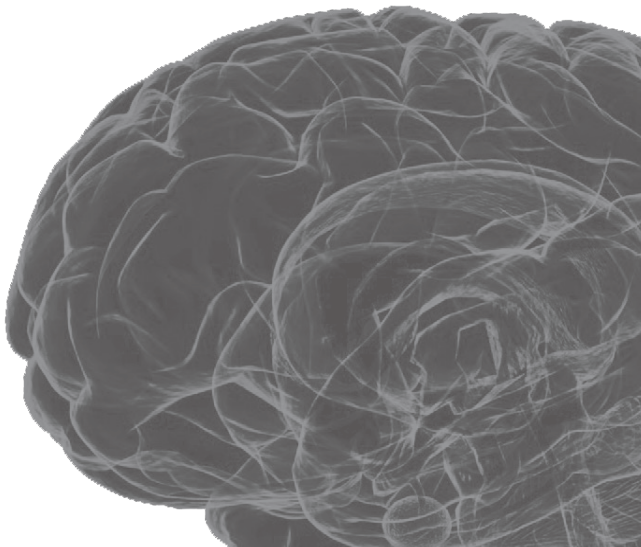

INTRODUCTION

Computerized neuropsychological test (CNT) batteries have become increasingly popular in clinical and research settings over the past years. A major advantage of CNT's is the potential of having computers perform labor-intensive test administration, and accurate as well as less time consuming scoring procedures. The Central Nervous System Vital Signs (CNS VS; (1)) is a battery composed of CNTs that are mostly based on well-established conventional paper-and-pencil tests. CNS VS has been shown to be well suited for use as a brief clinical screening tool for cognitive dysfunction in different patient groups (1-3).

However, in spite of their widespread use and clinical utility, many CNT's, including CNS VS, are limited in terms of their psychometric development, and stratified norms are often lacking (4, 5). Most of the normative data have been collected and described by Gualtieri and Johnson (1) more than a decade ago based on a sample of 1,069 volunteering American participants ranging in age from 7 to 90 years. Since 2006, the normative database has been expanded to over 1,900 participants (http://www.cnsvs.com), but unfortunately no information on the updated CNS VS normative database has been reported to date. As a result, there is no publically available description of the composition of the American sample regarding background characteristics, nor the basis on which participants were classified as "normal," except that they had "no past or present neurological or psychiatric disorder, head injury, and learning disabilities" (1). Hence, the representativeness of the norms for the American population cannot be evaluated and is uncertain. Moreover, although the CNS VS has been translated into over 50 languages, only normative data for the American version has been published. However, the performance on translated versions of the CNS VS could be affected by cultural influences rendering the norms for the American sample inapplicable to individuals in other countries. To the best of our knowledge, the applicability of the original norms to non-American samples has never been studied. In addition, the original CNS VS norms may be outdated, since norms were based on data that were collected over a decade ago. Ageing of norms is an important treat to the usefulness of normative data (e.g., (6)).

Another limitation of the original CNS VS' normative data concerns the absence of adjustments for effects of education and sex, as normalized scores are solely age-corrected. All 3 sociodemographic variables (i.e., age, education, and to a lesser extent sex) have extensively been found to correlate with performance on various neuropsychological tests (7, 8), including performance on computerized tests (9-11). The absence of corrections for these variables when interpreting performance on neuropsychological tests hinders proper interpretation and comparison in terms of cognitive functioning.

In the current study, we evaluated the performance of a sample of healthy Dutch participants on the CNS VS against the original American normative data. In addition, we evaluated the impact of the sociodemographic variables age, education, and sex on performance using a regression-based procedure. By using this approach, individual normed scores can be derived. Formulae for obtaining sociodemographically adjusted normed scores based on normative data from the Dutch population are presented as well.

METHOD

Participants and Procedure

A total of 158 Dutch participants, recruited by convenience sampling from the broad network of the research group, volunteered to participate in the study. Participants were considered healthy if (a) there was no past or present psychiatric or neurologic disorder; (b) they had no other major medical illnesses in the past year prior to participation (e.g., cancer, myocard infarct);

(c) they were free of use of any centrally acting psychotropic medication; and (d) did not have a history of or current alcohol or drug abuse. The computerized neuropsychological tests were, depending on participants' preference, administered individually at Tilburg University (Tilburg, The Netherlands), Elisabeth-TweeSteden Hospital (Tilburg, The Netherlands), or at participants' homes. Well-trained test technicians ensured appropriate conditions and remained present during the entire assessment. Participants provided written informed consent and filled out a questionnaire on health status.

The study was approved by the Medical Ethics Committee Brabant, The Netherlands (File number: NL41351.008.12).

Table 1 Description of educational levels

Level	Verhage categories [a]
Low	1. Less than 6 years of primary education 2. Finished primary education 3. Primary education and less than 2 years of low-level secondary education 4. Finished low-level secondary education
Middle	5. Finished average-level secondary education
High	6. Finished high level secondary education 7. University degree

[a] Adapted from Verhage (12)

Measures and Normative Data

Sociodemographic Characteristics. Number of years and completed level of education were self-reported by participants. Grade retention did not count as an extra year, neither did supplementary vocational courses that were attended after graduation. Actual number of years of education was verified (i.e., recalculated by the test technician together with the participant) during the assessment. To classify the level of education, the Dutch Verhage scale was used (12). Its 7 categories were merged into 3 ordinal categories: low educational level (Verhage 1 until 4), middle educational level (Verhage 5), and high educational level (Verhage 6 and 7; Table 1). Participants also rated their frequency of computer use on a 3-point scale with categories never, some, or frequent.

Central Nervous System Vital Signs. Cognitive functioning was assessed using the Dutch translation of the CNT battery CNS VS. It comprises 7 neuropsychological tests, yielding measures of performance in 11 cognitive domains. Since some domains scores generated by CNS VS are very similar (i.e., mainly calculated based on components of the same tests), we chose to consider only 7 cognitive domains (Table 2). Time needed to complete the total battery is approximately 30 to 40 minutes. Scoring is automated and scores are presented in raw and normed scores, as well as percentile ranks, generating a summary report for clinical interpretation or statistical analysis. Raw scores include the number of correct or incorrect responses, reflecting accuracy, and mean reaction times (in milliseconds) on individual tests and domains, reflecting speed. Normed scores are automatically generated by the CNS VS and represent the performance of an individual relative to the American normative sample controlled for age. In the population, CNS VS normed scores are assumed to have a mean of 100 and a standard deviation of 15; higher scores always indicate better performance (1). The percentile rank of these scores refer to the proportion of scores in the

normative sample that are equal to or lower than the score at hand. All testing was done using CNS VSX' local software app, on the same type of laptop computers running Windows 7 Professional on 64-bit operating systems. Background programs were shut down at time of all assessments and laptops were disconnected from (wireless) internet resources.

There is not a large body of literature regarding the reliability and validity of CNS VS. In the original reliability and validity paper, Gualtieri and Johnson (1) describe CNS VS' psychometric characteristics to be very similar to the characteristics of the conventional neuropsychological tests on which the battery is based. However, correlational studies suggest at best moderate correlations between CNS VS and traditional neuropsychological tests, and in addition, no consistent clear patterns of convergent or discriminant validity have been determined (1, 9, 13-15). As no 2 presentations of CNS VS are similar due to the random presentation of stimuli, the battery is assumed to be suitable for serial administration without inducing practice effects.

Table 2 Supplementary material on central nervous system Vital Signs (CNS VS)

Cognitive domain	CNS VS test	Domain score calculations ("Formulas for Calculating Domain Scores," n.d.) (16)	Description
Verbal memory	Verbal memory test (VBM)	VBM direct correct hits + VBM direct correct passes + VBM delayed correct hits + VBM delayed correct passes	Learning a list of 15 words, with a direct recognition, and after six more tests a delayed recognition trial
Visual memory	Visual memory test (VIM)	VIM direct correct hits + VIM direct correct passes + VIM delayed correct hits + VIM delayed correct passes	Learning a list of 15 geometric figures, with a direct recognition, and after six more tests a delayed recognition trial
Processing speed	Symbol digit coding (SDC)	SDC correct responses—SDC errors	Number 1 to 9 correspond to different symbols. As many correct numbers as possible have to be filled out underneath the presented symbols in 90 seconds
Psychomotor speed	Finger-tapping test (FTT); SDC	FTT taps right hand + FTT taps left hand + SDC correct responses	Pressing the space bar with the index finger as many times in 10 seconds, above mentioned
Reaction time	Stroop test (ST)	(ST Part II reaction time on correct responses + ST Part III reaction time on correct responses)/2	In Part I, pressing the space bar as soon as the word RED, YELLOW, BLUE, and GREEN appear—In Part II, pressing the space bar as the color of the word matches what the word says—In Part III, pressing the space bar as the color of the word does not match what the word says
Complex attention	Continuous performance test (CPT); Shifting attention test (SAT); ST	Stroop commission errors + SAT errors + CPT commission errors + CPT omission errors	Responding to a target stimulus "B" but no any other letter. Shifting from one instruction to another quickly and accurately (matching geometric objects either by shape or color); Above mentioned

Statistical Analysis

Mean Domain and Test Performance. To explore whether mean CNS VS performance of the Dutch participants differed from the mean performance of the normative American sample, a series of two-tailed one-sample *Z*-tests was performed (M = 100, SD = 15). CNS VS presents up to 10 different mean raw scores (i.e., for each of the 10 different age-groups of CNS VS' normative sample) for each domain and test. Since adopting the same subgroups in the Dutch sample would dramatically decrease the sample size for these analyses, the automatically generated age corrected normed scores were used in all comparisons between the American and Dutch samples. In this way, we also account for effects of age in both groups. Effect sizes (ES) for potential differences between the American and the Dutch samples were calculated and expressed as Cohen's d using pooled variance. ES between ≤ .20 and .49 were defined as small, between .50 and .79 as medium, and ≥ .80 represented large effects (17).

Multiple Regression Analyses. To explore the effects of sociodemographic factors on CNS VS performance, a series of multiple linear regression analyses was conducted using raw CNS VS domain scores as the outcome variables and a predetermined list of sociodemographic predictors. Age (in years), education (dummy coded; middle education as reference category), and sex (coded as 0 = men, 1 = women) were predictor variables which were entered as a single block ("enter" method). Assumptions were evaluated as follows: independence of observations was evaluated by Durbin–Watson tests (18), and linearity and homoscedasticity were examined using scatter plots of residuals. Potential multicollinearity between predictors was examined by inspecting Pearson's correlation coefficients. By computing Cook's distances, univariate influential cases were identified (19). Normality of residuals was investigated by visual inspection of histograms. Alpha was set at .02 in order to prevent the problem of inflated Type I errors related to multiple comparisons. All statistical analyses were performed with SPSS 22.0.

Normative Regression Formulae. The results of the regression models which regresses performance on age, sex, and educational level also provide the formulae for computing sociodemographically adjusted norms. Clinicians and researchers can use these formulae in future administrations of CNS VS to obtain normed scores for individuals on each cognitive domain, based on their age, educational level, and sex. In particular, all predictors were included in the normative formulae irrespective of the significance of the effect, as follows:

$$Y_{p\ domain} = \alpha + b_1 Age + b_2 D_{low\ education} + b_2 D_{high\ education} + b_3 Sex$$

In this formula, $Y_{p\ domain}$ is the predicted raw domain score, α is the intercept, and b_1 trough b_3 are the regression coefficients. Notice that educational level is a categorical variable with 3 categories and therefore modeled by means of 2 dummy variables, 1 for low education and 1 for high education (i.e., middle education as reference category). Sex is also a dummy variable, with men as the reference category (i.e., for men: sex = 0 and for women: sex = 1). Application of these regression formulae is demonstrated in Box 1.

Box 1 Application of sociodemographically adjusted normative formulae and a real-life example

1. Complement the formula: $Y_{p\ domain_a} = \alpha + b_{1\ age} + b_{2\ low\ education} + b_{2\ high\ education} + b_{3\ sex}$, with the assessed individual's age, education, and sex: this will result in a *predicted raw score* (Y_p) for each cognitive domain.	Consider a 68-year-old male patient who completed a high educational level, and obtained a raw score of 27 on processing speed. His predicted raw score for processing speed is $Y_{p\ processing\ speed} = 77.38 + (-0.52 * age) + (-3.16 * education_{low} + 3.98 * education_{high} + 2.42 * sex_{woman})$, with age = 68, $education_{low} = 0$, $education_{high} = 1$, $sex_{woman} = 0$, resulting in $Y_{p\ processing\ speed} = 46$.
2. Subtract the predicted raw score from the individual's obtained (Y_o) raw score, now a *difference score* is generated: $Y_o - Y_p$.	The predicted raw score = 46, subtracted from the obtained raw score (27) results in a difference score of −19.
3. The individual's *Z*-score is computed as follows: $Z\text{-score} = Y_o - Y_p / SD_{residual}$, where $SD_{residual}$ is the *SD* of the sample's residual, reflecting the accuracy of predictions made by the regression line.	Dividing the difference score by the $SD_{residual}$ of processing speed = 8.88 (see Table 6), results in $Z = -19/8.88 = -2.14$.
4. The *Z*-score can be interpreted via a *Z* distribution. As higher raw scores on reaction time and complex attention indicate worse performance, *Z*-scores for these domains have to be multiplied by −1 to facilitate consistent interpretation of *z* over all cognitive domains (i.e., positive *Z*-scores indicate a higher obtained raw score relative to others of similar age, education, and sex, and vice versa for negative *Z*-scores).	With a *Z*-score of −2.14, performance on processing speed is more than 2 *SD* lower than expected given the patients' age, education, and sex, which indicates *(serious) impairment*. The obtained raw score of this patient is represented by a CNS VS (age corrected) normed score of 78 (labeled by CNS VS as "below the expected level"), corresponding to a *Z*-score of: 78−100/15 = −1.47 (as compared to −2.14).

Note. CNS VS=Central Nervous System Vital Signs

[a]Age in years, sex: 0=man, 1=woman; education: low ($education_{low}$=1, $education_{high}$=0), middle ($education_{low}$=0, $education_{high}$=0), and high ($education_{low}$=0, $education_{high}$=1)

RESULTS

Sociodemographic Characteristics

Table 3 shows participants' sociodemographic characteristics. Mean age was 45.9 (*SD* = 14.4) years, ranging from 20.0 to 80.0. There was a female predominance (57%) in the Dutch sample, which appears comparable to the American normative database of CNS VS. The participants completed 16.9 years of education on average. Almost all participants (97%) indicated to use the computer frequently. Men and women did not differ in terms of mean age, $t(156) = 0.48$, $p = .162$, and educational level, $\chi^2(2) = 1.20$, $p = .550$, neither did men and women differ in frequency of computer use, $\chi^2(2) = 1.42$, $p = .491$. Likewise, no significant differences between groups based on the 3 educational levels were found concerning age, $F(2, 155) = 1.04$, $p = .355$, and frequency of computer use, $\chi^2(4) = 8.79$, $p = .067$.

Table 3 Sociodemographic characteristics of the Dutch sample (N = 158) and the American sample (N = 1,069)

	Dutch sample	American sample [a]
Age, years, *M* ± *SD*	45.94 ± 14.43	Unknown [a]
Range	20-80	7-90
Sex, N (%)		
Women	90 (57.0)	654 (61.2)
Men	68 (43.0)	415 (38.8)
Education		
Years, M ± *SD*	16.88 ± 3.29	Unknown [a]
Level, N (%)		
Low	19 (12.0)	Unknown [a]
Middle	57 (36.1)	Unknown [a]
High	82 (51.9)	Unknown [a]
Computer use, N (%)		
Never	1 (0.6)	288 (26.9)
Some	4 (2.5)	52 (4.9)
Frequent	153 (96.8)	729 (68.2)

[a] Characteristics of the American sample were not presented for the sample as a whole (see Gualtieri and Johnson (1) for demographic characteristics across different age groups)

Mean Domain and Test Performance

Table 4 shows mean differences for the Dutch sample as compared with the American-based normed scores (M = 100, SD = 15). Significant mean differences were found for the domains of processing speed (mean difference = 4.52, SD = 14.48; z = 3.77, p < .001), psychomotor speed (mean difference = 7.17, SD = 12.87; z = 5.97, p <. 001), and cognitive flexibility (mean difference = 2.91, SD = 12.94; z = 2.39, p= .017), where the Dutch sample demonstrated higher scores than the American normative sample. ES were small (Cohen's d respectively .19 and .30 for cognitive flexibility and processing speed), except for psychomotor speed with a difference of near-medium size (Cohen's d = .49).

At the level of normed individual test scores (e.g., representing reaction time, number of correct answers), the Dutch sample demonstrated significantly higher scores on 5 out of 17 measures compared with the American normative sample (see Table 4). The number of correct rejections in the delayed recognition visual memory task was significantly higher in the Dutch sample, and Dutch participants performed significantly more taps on the Finger Tapping Test with both the right and the left hand. In addition, the numbers of correct responses on the Symbol Digit Coding task and Shifting Attention Task were higher in the Dutch compared with the original American normative group. A near-medium sized difference was found for the right hand Finger Tapping Test (Cohen's d = .46), for the other tests, ES were small (Cohen's d ranging from .20 to .36).

Table 4 Mean CNS VS normed scores of Dutch participants (N = 158) compared with the American normative data (*M* = 100; *SD* = 15)

	Mean (*SD*) [a]	Mean difference	*Z*-test	*p*	Effect size *d* [b]
Domain					
Verbal memory	98.66 (14.99)	−1.34	−1.11	.268	−.09
Visual memory	101.81 (12.98)	1.81	1.50	.133	.12
Processing speed	104.52 (14.48)	4.52	3.77	<.001*	.30
Psychomotor speed	107.17 (12.87)	7.17	5.97	<.001*	.49
Reaction time	101.41 (11.13)	1.41	1.17	.242	.09
Complex attention	101.88 (11.66)	1.88	1.54	.124	.13
Cognitive flexibility	102.91 (12.94)	2.91	2.39	.017*	.19
Test					
Verbal memory test					
Direct recognition correct hits	99.01 (14.66)	−0.99	−0.79	.425	−.07
Direct recognition correct rejections	100.94 (12.58)	0.94	0.76	.447	.06
Delayed recognition correct hits	98.16 (14.86)	−1.84	−1.48	.138	.12
Delayed recognition correct rejections	98.98 (14.07)	−1.02	−0.89	.370	.08
Visual memory test					
Direct recognition correct hits	99.50 (13.97)	−0.50	−0.40	.685	.03
Direct recognition correct rejections	102.53 (13.35)	2.53	2.05	.040	.17
Delayed recognition correct hits	98.46 (12.06)	−1.54	−1.25	.211	−.10
Delayed recognition correct rejections	103.86 (11.43)	3.86	3.13	.002*	.26
Finger-tapping test					
Number of taps right	106.79 (12.66)	6.79	5.52	<.001*	.46
Number of taps left	104.81 (12.99)	4.81	3.92	<.001*	.33
Symbol digit coding test					
Number correct	105.37 (14.27)	5.37	4.39	<.001*	.36
Stroop test					
Reaction time Part I	101.11 (10.01)	1.11	0.91	.364	.08
Reaction time Part II	100.48 (12.78)	0.48	0.39	.698	.03
Reaction time Part III	102.34 (10.48)	2.34	1.90	.057	.16
Shifting attention test					
Number correct	102.97 (14.16)	2.97	2.42	.016*	.20
Reaction time	100.51 (15.13)	0.51	0.42	.678	.03
Continuous performance test					
Number correct	101.67 (9.48)	1.67	1.37	.172	.12

Note. CNS VS = Central Nervous System Vital Signs

[a] CNS VS normed scores based on the American normative sample have a mean of 100 and a standard deviation of 15; higher scores indicate better performance; positive mean difference indicates better performance for the Dutch sample and vice versa

[b] Cohen's d effect sizes: ≤.20 to .49, small; .50 to .79, medium; ≥.80, large (17)

*p < .02

Multiple Regression Analyses

None of the assumptions regarding the regression analyses were violated. There was independence of residuals, with Durbin–Watson statistics ranging from 1.72 to 2.22. Scatter plots demonstrated linear relationships between the dependent and independent variables, and homoscedasticity. No problems with collinearity were identified, with correlations *r* between −.01 and .38. No influential cases were identified (all Cook's distances >1), and histograms demonstrated normally distributed standardized residuals for each cognitive domain.

Table 5 shows the results of the regression analyses. Overall, significant effects of age were found on performance in 4 out of 7 raw cognitive domains scores (i.e., for processing speed, psychomotor speed, reaction time, and cognitive flexibility). Higher age was consistently associated with lower scores. Educational level was significantly associated with performance on 3 out of 7 domains: participants with a high educational level (i.e., compared with a middle and low educational level) obtained higher scores on visual memory, processing speed, and cognitive flexibility. Sex was found to be significantly associated with performance on the verbal memory domain, in favor of women, and the psychomotor speed domain, in favor of men. The proportions of explained variances (R^2) by age, education, and sex ranged from 7.2% (for the verbal memory domain) up to 46.2% (for the processing speed domain). Hierarchical regression analyses demonstrated significantly more explained variance for a model including both age and education, compared with a model with solely age, in 4 out of 7 cognitive domains. In 2 out of 7 domains adding the factor sex on top of age and education resulted in significantly more variance explained. Adding education or sex (in addition to age) to the regression model significantly increased the explained variance for the cognitive domains, except for the reaction time domain, where only age contributes significantly (data not shown).

Table 5 Multiple regression based on the Dutch sample (N = 158): association of age, education, and sex with raw cognitive domain scores of CNS VS

Cognitive domain	Predictor	B	SE B	95% CI B		*p*	F(df)	R^2
				Lower limit	Upper limit			
Verbal memory						<.001*	2.91(4)	.072
	Age	−0.03	0.03	−0.08	0.03	.320		
	$Education_{low}$	−0.21	1.21	−2.61	2.18	.861		
	$Education_{high}$	1.49	0.79	−0.07	3.05	.062		
	Sex_{woman}	1.77	0.74	0.31	3.23	.018*		
Visual memory						<.001*	4.55(4)*	.108
	Age	−0.06	0.02	−0.10	−0.01	.021		
	$Education_{low}$	−0.92	1.12	−3.13	1.29	.415		
	$Education_{high}$	1.79	0.73	0.35	3.22	.015*		
	Sex_{woman}	0.83	0.68	−0.51	2.18	.222		
Processing speed						<.001*	32.83(4)*	.462
	Age	−0.52	0.05	−0.62	−0.42	<.001*		
	$Education_{low}$	−3.16	2.41	−7.91	1.60	.191		
	$Education_{high}$	3.98	1.56	0.92	7.06	.011*		
	Sex_{woman}	2.42	1.45	−0.45	5.29	.097		
Psychomotor speed						<.001*	24.49(4)*	.392
	Age	−0.87	0.09	−1.05	−0.68	<.001*		
	$Education_{low}$	0.22	4.5	−8.65	9.09	.960		
	$Education_{high}$	5.56	2.91	−0.18	11.31	.058		
	Sex_{woman}	−7.44	2.72	−12.82	−2.07	.007*		
Reaction time[a]						<.001*	6.22(4)*	.142
	Age	1.65	0.39	0.88	2.42	<.001*		
	$Education_{low}$	−11.43	19.09	−49.17	26.30	.550		
	$Education_{high}$	−20.51	12.11	−44.43	3.42	.092		
	Sex_{woman}	−20.71	11.36	−43.16	1.73	.070		
Complex attention[a]						<.001*	4.11(4)*	.100
	Age	0.03	0.02	−0.02	0.08	.189		
	$Education_{low}$	2.60	1.17	0.29	4.90	.027		
	$Education_{high}$	−1.30	0.73	−2.75	0.14	.076		
	Sex_{woman}	0.65	0.69	−0.70	2.01	.343		
Cognitive flexibility						<.001*	12.38(4)*	.249
	Age	−0.28	0.06	−0.40	−0.17	<.001*		
	$Education_{low}$	−6.16	2.82	−11.76	−0.57	.031		
	$Education_{high}$	5.05	1.81	1.48	8.62	.006*		
	Sex_{woman}	−1.63	1.69	−4.98	1.72	.337		

Table 5: note. CNS VS=Central Nervous System Vital Signs; *df*=degrees of freedom; *SE* B=standard error B; 95% CI B=95% confidence interval B. Coding of predictors: age in years; low level of education: $eduction_{low}$= 1, $education_{high}$= 0; middle level of education: $education_{low}$=0, $education_{high}$=0; high level of education: $education_{low}$=0, $education_{high}$=1; sex: man=0, woman=1

[a] Higher scores indicate lower performance

* p < .02

Normative Regression Formulae

Table 6 shows the regression formulae that can be used to calculate normed predicted scores (i.e., corrected for effects of age, education, and sex) on cognitive domains of CNS VS for the Dutch population. An example of the application of the sociodemographically adjusted normative formulae is shown in Box 1.

Table 6 Regression formulae based on the Dutch sample (N = 158).

Cognitive domain	Regression equation [a]	$SD_{residual}$
Verbal memory	50.93 + (−0.03 * age) + (−0.21 * $education_{low}$ + 1.49 * $education_{high}$) + (**1.77 * sex_{woman}**)	4.47
Visual memory	47.33 + (−0.06 * age) + (−0.92 * $education_{low}$ + **1.79 * $education_{high}$**) + (0.83 * sex_{woman})	4.12
Processing speed	77.38 + (**−0.52 * age**) + (−3.16 * $education_{low}$ + **3.98 * $education_{high}$**) + (2.42 * sex_{woman})	8.88
Psychomotor speed	219.00 + (**−0.87 * age**) + (0.22 * $education_{low}$ + 5.56 * $education_{high}$) + (**−7.44 * sex_{woman}**)	16.58
Reaction time[b]	590.03 + (**1.65 * age**) + (−11.43 * $education_{low}$ + −20.51 * $education_{high}$) + (−20.71 * sex_{woman}) * −1	69.03
Complex attention[b]	5.07 + (0.03 * age) + (2.60 * $education_{low}$ + −1.30 * $education_{high}$) + (0.65 * sex_{woman}) * −1	4.13
Cognitive flexibility	58.51 + (**−0.28 * age**) + (−6.16 * $education_{low}$ + **5.05 * $education_{high}$**) + (−1.63 * sex_{woman})	10.21

Note. Age in years, sex: 0 = man and 1 = woman; education: low ($education_{low}$ = 1, $education_{high}$ = 0), middle ($education_{high}$ = 0, $education_{low}$ = 0), and high ($education_{low}$ = 0, $education_{high}$ = 1). $SD_{residual}$ = standard deviation of the sample's residual. $p < .02$ in bold

[a] $Y_{p\ domain} = – + b_1Age + b_2D_{low\ education} + b_2D_{high\ education} + b_3Sex$. [b] Higher scores indicate lower performance

DISCUSSION

We examined the performance of a group of healthy Dutch participants who underwent neuropsychological examination with the computerized neuropsychological battery CNS VS. The purpose of this study was threefold: (a) to examine the applicability of the American CNS VS norms for the Dutch population; (b) to examine the effects of age, education, and sex on CNS VS performance of the Dutch sample; and (c) to provide sociodemographically adjusted normative formulae for the Dutch population.

At the level of individual CNS VS tests, scores in the Dutch sample were significantly higher on 5 out of 17 measures. Consequently, differences in mean performance for 3 out of 7 cognitive domains were found between the Dutch sample and the American normative sample; in the 2 domains covering different types of speed, namely processing and psychomotor speed, and in cognitive flexibility.

It should be noted that computer skills - including keyboard work and on - screen visual scanning - have improved tremendously over the past decade, which may result in improvements in overall performance on computerized neuropsychological speed tests. Indeed, an earlier study on computer familiarity and CNS VS performance demonstrated significantly better (i.e., faster) performance in people who are very familiar with computers, opposed to people who reported only "some" familiarity with computers (20). As can be expected from the more frequent use

of computers nowadays, our sample comprised too few participants with only some or none computer familiarity to look into these effects. The beneficial effects of computer familiarity may (partly) explain the differences between the American 2006 group and the Dutch 2016 group.

In addition, a possible Flynn effect should be considered given the headspring of the normative data presented by CNS VS. The Flynn effect refers to a substantial rise of the population's performance on tests of intelligence in developed countries, typically about 3 to 5 points (i.e., on a IQ scale with a mean of 100 and standard deviation of 15 points) per decade. Explanations for the Flynn effect include genetic, environmental, methodological, and measurement factors (21, 22). It has been found that the impact of the Flynn effect extends beyond the measurement of IQ and has, for example, been demonstrated on measures of memory (23, 24), processing speed, and cognitive flexibility (25), with gains comparable to the size of the Flynn effect on measures of IQ. The scale of normed scores of CNS VS tests and domains is similar to that of IQ points, and the original normative data presented by Gualtieri and Johnson (1) have been established over a decade ago. Therefore, mean normed cognitive domain scores can be expected to be about 3 to 5 points higher in the current 2015/2016 sample than the original normative data—which corresponds to the increased scores found in the present study.

Since the total variance explained by the sociodemographic variables added up to almost 50% in the present study (i.e., in particular for the processing speed and psychomotor speed domain), the influence of age, sex, and education should be taken into consideration when interpreting performance on the CNS VS. CNS VS incorporated corrections for age in their normative evaluation, but did not correct for effects of education and sex. Consistent with the literature, higher age was associated with lower performance (26). Educational level was found to be positively associated with performance on visual memory, processing speed, and cognitive flexibility. Highly educated participants are likely to be somewhat overrepresented in our Dutch sample relative to the general Dutch population (CBS Statistics Netherlands, http://statline.cbs.nl/ Statweb/). Although the higher performance of the sample might also be explained by this factor, we have no information on education in the original American normative sample, as these data are not disclosed by the authors. We may assume that this sample also included a relatively high proportion of highly educated participants, as these are typically (more) interested in study participation (27). As would be expected, sex did not play a large role, except for the verbal memory domain favoring women, and the psychomotor speed domain favoring men. These findings are consistent with literature on sex differences in performance on other (computerized) tests (10, 28, 29), and reported by Gualtieri (30) who examined sex differences in a subset of participants who completed the CNS VS battery during its standardization study.

Based on the collected data, we established regression-based normative formulae to adjust for the effect of sociodemographic variables on CNS VS performance. In future evaluations of performance in our (Dutch) patient studies, these normative data will replace the American norms.

Some critical remarks are in order with respect to the current study. Presented results are based on performance in Dutch healthy participants recruited on availability (i.e., convenience sampling). A disadvantage of this method includes the risk that the sample might not represent the Dutch population as a whole. As stated above, a relatively small number of low-educated participants (i.e., 12% compared with approximately 35% in the general Dutch population (CBS Statistics Netherlands, http://statline.cbs.nl/ Statweb/) was included in the present study. The regression-based method requires smaller samples since continuous covariates do not have to be categorized (e.g., stratifying the sample into groups of different age, sex, and educational levels). Instead, it makes optimum use of the entire sample to estimate the normative statistics

and the regression model (31, 32). However, one should always be careful when using these data for interpreting individual test performance of people who are in the extreme ends of age, or education (very low levels, or by contrast, very high levels of education). In addition, data were collected using a Dutch translation of the CNS VS battery. Since the equivalence with the English version of the test has never been confirmed, we cannot rule out that differences in difficulty due to translation of instructions and items also have a share in the observed differences (33). Although our results may not be generalizable to other countries or to populations who speak other languages, they demonstrate that CNS VS users from other populations than the American should use and interpret the original norms with caution. Moreover, we recommend on considering adjusting for sociodemographic factors when interpreting CNS VS performance in American populations.

Also, changes in technology (i.e., computer hardware/ software) since the collection of the initial American norms may have affected important parameters including timing accuracy. Although technical aspects and settings of the devices used in the present study were the same for all assessments, no information is available concerning devices that were used when collecting the American normative data. Differences therein might explain a small portion of the group differences in our study, but this is unlikely considering the generally rather small timing inaccuracies and the significant differences that we demonstrated for cognitive domains (34, 35). Yet, although the timing precision of CNS VS on different test systems should be explored in more detail, CNS VS provides explicit recommendations concerning system requirements for installation, and states that their applications are designed to be working equally well over types of devices and types of applications ('CNS Vital Signs Optimal Use Installation Guide', http://www.cnsvs.com). However, evidence of this statement is not available.

Future studies should consider the psychometric robustness of CNS VS across cultures and (other) non-American languages. Furthermore, various clinical and research settings require repeated neuropsychological assessment, for example, for the evaluation of effects of intervention on cognitive functioning. This emphasizes the need for inspection of CNS VS regarding repeated assessment, addressing practice effects (i.e., improvements in performance due to familiarity with the test, its items, and test procedures opposed to true cognitive improvement). Currently, we are performing follow-up assessments in the same Dutch sample with the aim of establishing change indices correcting for potential practice effects and measurement errors to determine "true" (i.e., reliable) clinically meaningful cognitive change when administering CNS VS repeatedly over time.

The present study examined the applicability of the original American normative data of CNS VS to a non-American population: our results call the usefulness of the 2006 norms of the CNS VS in other populations than the American into question. Furthermore, we identified effects of education and sex, in addition to known effects of age, on CNS VS performance. These findings highlight the need for more up-to-date population-based norms for CNS VS performance. Sociodemographic factors should be considered when interpreting performance on this measure, for example, by applying sociodemographically adjusted normative formulae, as we have presented here.

NOTE

$$M_1 - M_2 \,/\, SD_{\text{pooled}}, \quad \text{with } SD_{\text{pooled}} = \sqrt{\left(n_1 - 1\right)SD_1^2 + \left(n_2 - 1\right)SD_2^2 \,/\, \left(n_1 - 1\right) + \left(n_2 - 1\right)}$$

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CHAPTER 6

Cognitive outcomes in meningioma patients undergoing surgery: individual changes over time and predictors of late cognitive functioning

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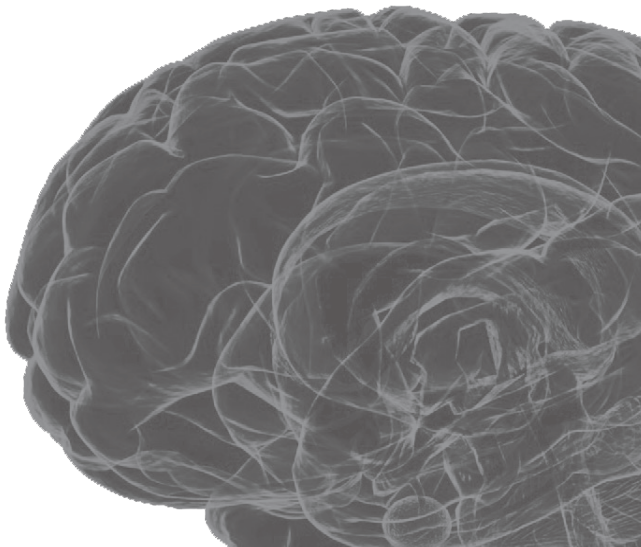


INTRODUCTION

The vast majority of patients with intracranial meningioma can be cured by surgery (1). However, meningioma patients suffer from deficits in several cognitive domains already before surgery (2). Surgical resection of the meningioma has been found to improve cognitive performance of patients, but post-operative cognitive deficits continue to exist, as significant cognitive impairments are reported up to 4 years after surgery (2-11). However, pre-operative cognitive functioning is often not examined, thereby limiting statements about changes in cognitive performance over time to date. The few studies that explored changes over time (following a pre-operative assessment, up to 9 months after surgery) predominantly demonstrated improved cognitive performance (6-10, 12, 13). Yet, study results were presented on the group instead of individual patient level, fairly simple measures of change in performance were adopted (e.g., raw difference scores), and practice effects of repeated assessments were often not corrected for (14).

Despite the fact that extensive cognitive deficits in meningioma patients have been described in a number of studies, research into predictors of cognitive performance in these patients remains limited (2). Mixed findings were reported with respect to the association between cognitive performance and, amongst others, tumor location and psychological factors (i.e., anxiety and depression) (2, 3, 5, 13, 1 5). Moreover, pre-operative predictors of late cognitive performance have only minimally been addressed in meningioma patients, which is remarkable given the negative impact of cognitive deficits on, for example, returning to social and professional activities after meningioma surgery (5, 16, 17). Information on the sociodemographic, clinical, psychological or cognitive characteristics of patients who are at risk for cognitive impairment on the long-term after surgery may help to inform patients and clinicians at an earlier stage.

We explored cognitive functioning using a computerized neuropsychological battery in a large sample of meningioma patients before, and 3 and 12 months after surgery. Changes in performance were assessed at the group level as well as at the individual level using reliable change indices (RCIs) for each of the 2 time intervals. Additionally, we sought to identify pre-operative predictors of late (i.e., 12 months post-operative) cognitive performance.

MATERIALS AND METHODS

Design

The present study was part of a prospective longitudinal study in which brain tumor patients admitted for surgical resection between November 2010 and June 2017 underwent neuropsychological assessment (NPA) 1 day before surgery (T0) and 3 months after surgery (T3) as part of standard clinical neuro-oncological care. A (approximately) 12 months post-operative follow-up assessment (T12) was added as from January 2014 for research purposes in order to explore long-term cognitive functioning.

Patients

Cases eligible for the current study were patients who underwent initial surgical resection, and who were, based on tissue obtained during surgery, histopathologically diagnosed with a WHO grade I or II meningioma. We excluded patients under the age of 18 years, with a history of intracranial neurosurgery, with intraosseous meningioma, with a recent history (≤ 2 years) of severe psychiatric or neurologic disorders, other major medical illnesses in the past year prior to surgery (e.g., cancer), a lack of basic proficiency in Dutch, or/and with the inability to undergo the NPA due to severe visual, motor, or cognitive problems. In addition, patients who participated in the cognitive rehabilitation studies that were simultaneously running at the Elisabeth-TweeSteden hospital were

excluded from the current study if they had been randomly assigned to the intervention (i.e., rehabilitation) group (18, 19). The cutoff for the time-interval between T0 and T12 assessment was set at a maximum of 21 months.

All patients provided written informed consent. The study was approved by the Medical Ethics Committee (file number NL41351.008.12). The patient sample of the current study includes 68 patients that were also included in a previous study (9, 20).

Measures and procedure

Sociodemographic characteristics. Patients were assessed per standardized protocol at all 3 time-points, including a checklist and standardized interview at T0 (i.e., for obtaining and verifying sociodemographic information such as age, sex, and educational level). The highest completed level of education was classified according the Verhage scale (21). Its 7 categories were merged into 3 categories: low educational level (Verhage 1 until 4), middle educational level (Verhage 5), and high educational level (Verhage 6, 7).

Clinical characteristics. Clinical information (e.g., data on medication use) was obtained from the electronic medical charts. A histopathological diagnosis was provided following surgery and categorized as WHO grade I meningioma or WHO grade II meningioma (22). By means of a pre-operative contrast-enhanced T1 weighted Magnetic Resonance Image tumor location, i.e., supratentorial versus infratentorial, and further classified as frontal (i.e., frontal, frontal-temporal, and frontal-parietal) versus non-frontal involvement, lesion side (i.e., right, left, bilateral), and the number of tumors were identified. In addition, total tumor volume (in mm^3, of the meningioma which was operated on) was determined using semi-automatic segmentations performed in ITK-snap (23), followed by minor manual adjustments to lesion margins. The American Society of Anesthesiologist (ASA) score was considered as a physical status classification, ranging from ASA I (patient completely healthy) to ASA V (moribund patient) (24). ASA score was considered dichotomous: patients within ASA categories I and II were considered healthy, whereas patients within category III and IV were considered as patients with substantial comorbidities. Medication use was classified as the use of anti-epileptic drugs and/or corticosteroids.

Psychological characteristics. Anxiety and depression were assessed using the Dutch translation of the Hospital Anxiety and Depression Scale (HADS) (25, 26). This self-report screening instrument consists of 14-items: each subscale (i.e., anxiety and depression) includes 7 items with response options ranging from 0-3, resulting in a score from 0-21 for each subscale, with higher scores representing more anxiety/depression symptoms. The Dutch translation of the HADS has good psychometric qualities, with Cronbach's alphas of .81-.84 and .71-.86 for the anxiety and depression subscales respectively (26).

Cognitive performance. The formal Dutch translation of the computerized neuropsychological battery CNS VS was used to examine cognitive performance. CNS VS comprises 7 neuropsychological tests, yielding measures of performance in 11 cognitive domains (27). Since the measures of performance in some domains are largely based on scores on the same tests, we only consider the following 7 cognitive domains in the current study: verbal memory, visual memory, processing speed, psychomotor speed, reaction time, complex attention, and cognitive flexibility. The NPA's were performed using the CNS VSX local software app, on a laptop running a 64-bit operating system. A well-trained test technician remained present during each assessment.

After completing the battery, which takes approximately 30 - 40 minutes, raw scores for each cognitive domain amongst others are automatically provided by the program. Since effects of age, education, and sex were demonstrated on CNS VS performance in a Dutch normative sample (N = 158; age ranging from 20 to 80, education ranging from 10 to 26 years, assessed using CNS VS at baseline, and 3- and 12-months follow-up), raw cognitive domain scores were converted into sociodemographically-adjusted *Z*-scores (see Rijnen et al. (28) for a detailed description). In addition, effects of practice were found in the Dutch normative sample between the baseline and 3-month follow-up assessment. Test scores at T3 and T12 were therefore corrected for practice effects, in addition to the sociodemographic corrections (29).

Statistical analyses

Patients' characteristics. Descriptive and comparative analyses (i.e., one sample *Z*-tests and Chi-square tests of independence) were performed to explore potential differences in baseline sociodemographic, clinical, and psychological variables of the different patient samples assessed at T0, T3, and T12.

Pre- and post-operative cognitive performance. Cognitive performance in individual patients was defined as impaired if the *Z*-score was ≤ -1.50 (30). The numbers and percentages of patients scoring impaired were calculated for each cognitive domain at all time-points. In addition, a Chi-square test of independence was conducted to compare the proportion of meningioma patients with impaired performance (per domain, per time-point) to the proportion of participants in the normative sample with deviant performance (i.e., to test whether deviant scores occurred significantly more frequently in meningioma patients than in controls).

To explore mean performance on the 7 CNS VS cognitive domains of meningioma patients as compared to the normative controls at T0, T3, and T12, one-tailed one-sample *Z*-tests were performed (test values: mean (*M*) *z* = 0, standard deviation (*SD*) = 1). The mean *Z*-score for each cognitive domain (i.e., the difference between the patient sample and the normative sample in terms of *SD*s) equals Cohen's *d* effect size (ES) when calculated according the following formula: $Mean_{patients}$-$Mean_{controls}$/$SD_{controls}$. Therefore, mean *Z*-scores were considered as ES, with ES ≤ .50, between .51 and .79, and ≥ .80 respectively reflecting small, medium, and large effects (31).

Changes in individual and group cognitive performance over time. Changes in cognitive performance over time in individual patients were examined using RCIs. RCIs illustrate changes in performance in individual patients, compared to changes in performance of controls, which prevents us from overlooking individual changes that are masked when considering changes at the group level. RCIs also allow corrections for methodological phenomena such as practice effects and imperfect test-retest reliabilities. A standardized regression-based RCI as described by Maassen, Bossema, and Brand (32) was adopted. Rijnen and colleagues (29) described details with regard to the RCI for changes in CNS VS performance specifically, based upon results on repeated testing in a Dutch normative sample from baseline (N = 158) to 3- (N = 133) and 12-month (N = 77) follow up. In the current study, change was defined as RCI values exceeding ±1.645 (corresponding with a two-tailed alpha of .10%, 90% confidence interval), with positive values indicating improved performance and negative values representing declines. The numbers of patients with improved, stable, and declined performance were counted for each cognitive domain at the 2 time intervals. Additionally, Chi-square tests of independence were conducted for the separate cognitive domains to compare the proportion 'changers' (improvers or decliners) in the meningioma patients to the proportion

'changers' in the normative sample (i.e., again to test whether changes occurred significantly more frequently in patients than in controls). In case of significance, standardized residuals were used to interpret Chi-square tables as to which cells (i.e., which change category: improved, stable, declined) contributed to the significant result.

Changes over time (i.e., between T0-T3 and T3-T12) on the mean group level were assessed using the linear mixed effects models (LMEMs) that were fitted in order to identify pre-operative predictors of cognitive functioning (described in detail below) at T12.

Predictors of late cognitive impairment. LMEMs for repeated measurements were fitted to examine pre-operative predictors of late (T12) cognitive functioning in meningioma patients for each cognitive domain. To estimate the model parameters, the restricted maximum likelihood estimate method was used. The Aikaike Information Criterion and Bayesian Information Criterion were used to estimate model fit. A heterogeneous first-order autoregressive covariance structure was selected, the random effect was subject-ID, and predictors were entered as fixed effects into the model. Outcome measures were the *Z*-scores for the separate cognitive domains of CNS VS at T12. Predictors included measurement (i.e., T0, T3, T12), sociodemographic (i.e., age, sex, educational level), and clinical (i.e., tumor location: hemisphere, supra- versus infratentorial, frontal versus non-frontal, number of meningioma, tumor volume, ASA score, medication use), and psychological (i.e., HADS anxiety and depression) variables. In addition, T0 scores of all domains were included into the LMEMS as cognitive predictors except the T0 scores of the predicted domain itself. Including T0 performance of a specific domain itself as a predictor (in addition to the inclusion of T0 performance by assessing the fixed effect of measurement) as well, would result in the factor being incorporated twice in the model. A variance inflation factor of over 10 was used as cutoff for multicollinearity in the final models (33).

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 24.0, except for the construction of the LMEMs for which we used the *nmle* (34) package in R (35). To reduce false discovery rate due to multiple testing, *p*-values were set against a corrected alpha, using the Benjamini-Hochberg (BH) procedure (leaving much greater power than the Bonferroni technique) (36, 37). When performing the BH-procedure, individual *p*-values (i.e., per hypothesis) were put in order from smallest to largest: the smallest *p*-value has the rank of *i* = 1, the next smallest has *i* = 2, etc. Adjusted *p*-values were calculated by multiplying the original *p*-value by *(m/i)*, where *m* is the total number of tests for that hypothesis, and *i* the rank of the specific *p*-value. BH-adjusted *p*-values are then compared to the original alpha level of .05, and the rank of the largest adjusted *p*-value that is smaller than .05 is used to calculate an adjusted alpha level by following the formula: (*i/m)**.05 (36).

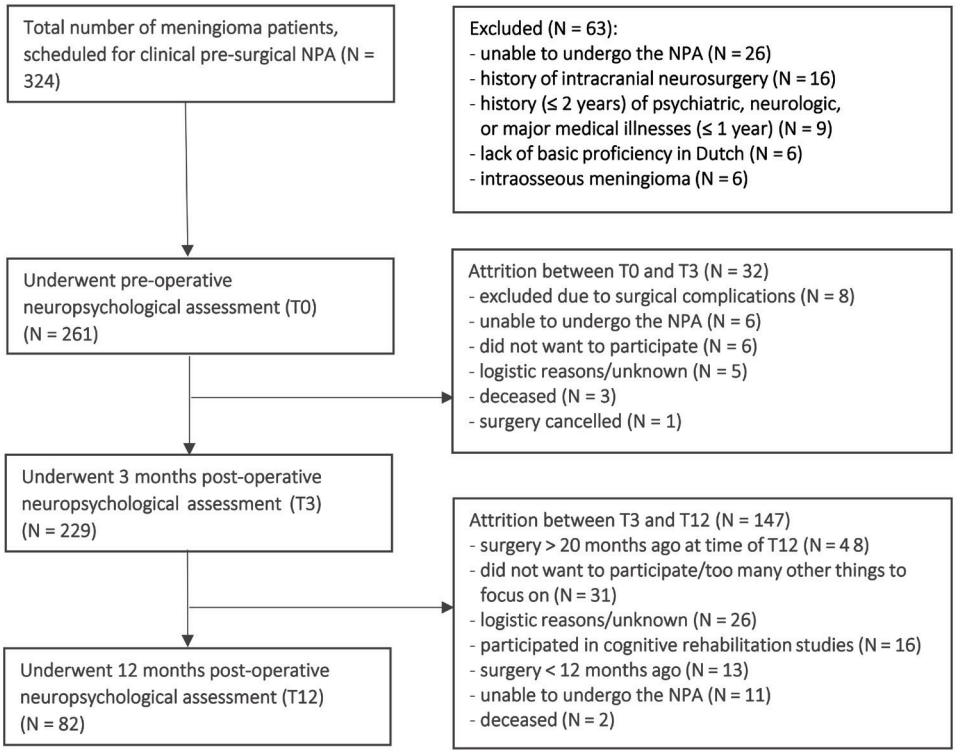
RESULTS

Patients' characteristics. Figure 1 shows the flow of meningioma patients through the current study. At T0, 261 patients were included. Thirty-two patients (12%) did not complete T3, resulting in 229 patients with a T0 and T3 assessment. Sixty-four percent of these patients did not undergo T12, mainly (i.e., in 33% of the patients) due to the later implementation of the long-term measurement. Eventually, 82 patients underwent a T0, T3, and T12 NPA. The median time interval between T0 and T3 was 2.83 months (ranging from 1.00 to 5.75 months). Median time interval between T0 and T12 was 12.42 months (ranging from 8.51 to 20.40 months).

Table 1 presents sociodemographic, clinical, and psychological characteristics of the meningioma samples over the 3 assessments. There were no significant differences between the

T0, T3, and T12 samples regarding sociodemographic, clinical, and psychological characteristics (*p*-values > BH-corrected alpha .002).

Figure 1 Flowchart of meningioma patients eligible for inclusion and follow-up



Pre- and post-operative cognitive performance. Prior to surgery, percentages of impaired patients ranged from 20.4% to 42.2% over domains (Figure 2). At T3 and T12 the percentages of patients scoring impaired on the cognitive domains respectively ranged from 16.7% to 32.6% and 13.8% to 22.5%. For 6 out of 7 domains at T0 and T3, and still 3 out of 7 domains at T12 after surgery, impairments were significantly more common in meningioma patients than in normative controls (*p*s < BH-corrected alpha of .04; Figure 2).

We found significantly lower mean performance in meningioma patients as compared to the normative sample on all cognitive domains at T0 (ES ranging from -0.54 to -1.53), T3 (ES ranging from -0.37 to -1.22), and T12 (ES -0.35 to -0.76) (*p*s < BH-corrected alpha of .05; Table 2). At T0 and T3, lowest mean *Z*-scores were found for complex attention (respectively -1.43 and -1.22) and reaction time (respectively -1.53 and -1.22). At T12, lowest mean scores were found for psychomotor Speed (-0.76), and again, reaction time (-0.65).

Table 1 Baseline sociodemographic, clinical, and psychological characteristics of samples of meningioma patients at each time-point

Baseline characteristics	T0 (N = 261)	T3 (N = 229)	T12 (N = 82)
Sociodemographic characteristics			
Age (years): mean ± *SD* (range)	57.8 ± 11.7 (23-82)	57.1 ± 11.7 (23-82)	55.9 ± 10.7 (32-75)
Education (years): mean ± *SD* (range)	13.7 ± 3.7 (6-26)	14.0 ± 3.7 (6-26)	14.4 ± 3.7 (8-26)
Sex: female/male N (%)	189(72) / 72(28)	167(73) / 62(27)	59(72) / 23(28)
Clinical characteristics			
WHO grade: I/II N (%)	240(92) / 21(8)	211(92) / 18(8)	76(93) / 6(7)
Number of meningioma: 1/≥2 N (%)	244(94) / 17(6)	217(95) / 12(5)	79(96) / 3(4)
Hemisphere: Left/right/bilateral N (%)	106(41) / 124(48) / 31(11)	94(41) / 107(47) / 28(12)	32(39) / 39(48) / 11(13)
Supratentorial/infratentorial N (%)	238(91) / 23(9)	208(91) / 21(9)	75(91) / 7(9)
Frontal/non-frontal N (%)	154(59) / 107(41)	135(59) / 94(41)	46(56) / 36(44)
Tumor volume (cm^3): median (range) [a]	33.5 (0.45-150.22)	32.0 (0.45-150.22)	34.5 (0.45-144.8)
ASA score: I,II/III,IV N (%)	225(86) / 36(14)	202(88) / 27(12)	71(87) / 11(13)
Use of medication: yes/no N (%) [b]	114(45) / 139(55)	100(44) / 123(54)	36(45) / 44(55)
Psychological characteristics			
Anxiety HADS: mean ± *SD* (range) [c]	7.2 ± 4.2 (0-20)	7.0 ± 4.2 (0-19)	7.0 ± 4.0 (0-17)
Depression HADS: mean ± *SD* (range) [c]	5.9 ± 4.6 (0-21)	5.7 ± 4.5 (0-21)	6.0 ± 4.9 (0-21)

WHO World Health Organization (20); ASA American Society of Anesthesiologists (21); AED antiepileptic drug; HADS Hospital Anxiety and Depression Scale (23)

[a] data missing T0 N = 30; T3 N = 24; T12 N = 6; [b] data missing T0 N = 8; T3 N = 6; [c] data missing T0 N = 32; T3 N = 25; T12 N = 7

Table 2 Cognitive performance on CNS VS domains of meningioma patients compared to the normative sample

	T0		T3		T12	
Domain	***Z*-score [a] M(*SD*)**	***Z*-test**	***Z*-score [a] M(*SD*)**	***Z*-test**	***Z*-score [a] M(*SD*)**	***Z*-test**
Verbal Memory	-0.67(1.30)	-10.38*	-0.90(1.35)	-13.50*	-0.59(1.19)	-5.29*
Visual Memory	-0.54(1.23)	-8.35*	-0.37(1.26)	-5.52*	-0.35(1.14)	-3.09*
Processing Speed	-1.11(1.36)	-17.39*	-0.85(1.22)	-12.75*	-0.58(0.99)	-5.22*
Psychomotor Speed	-1.31(1.66)	-20.45*	-0.93(1.36)	-13.95*	-0.76(1.14)	-6.72*
Reaction Time	-1.53(2.38)	-23.79*	-1.19(2.02)	-17.83*	-0.65(1.61)	-5.81*
Complex Attention	-1.43(2.60)	-21.61*	-1.22(2.29)	-18.06*	-0.61(1.92)	-5.43*
Cognitive Flexibility	-1.34(2.28)	-20.69*	-1.12(1.79)	-16.62*	-0.48(1.46)	-4.34*

* p < BH-corrected alpha .05

[a] Equals Cohen's d effect sizes where ≤ .50 = small, .51-.79 = medium, ≥ .80 = large (28)

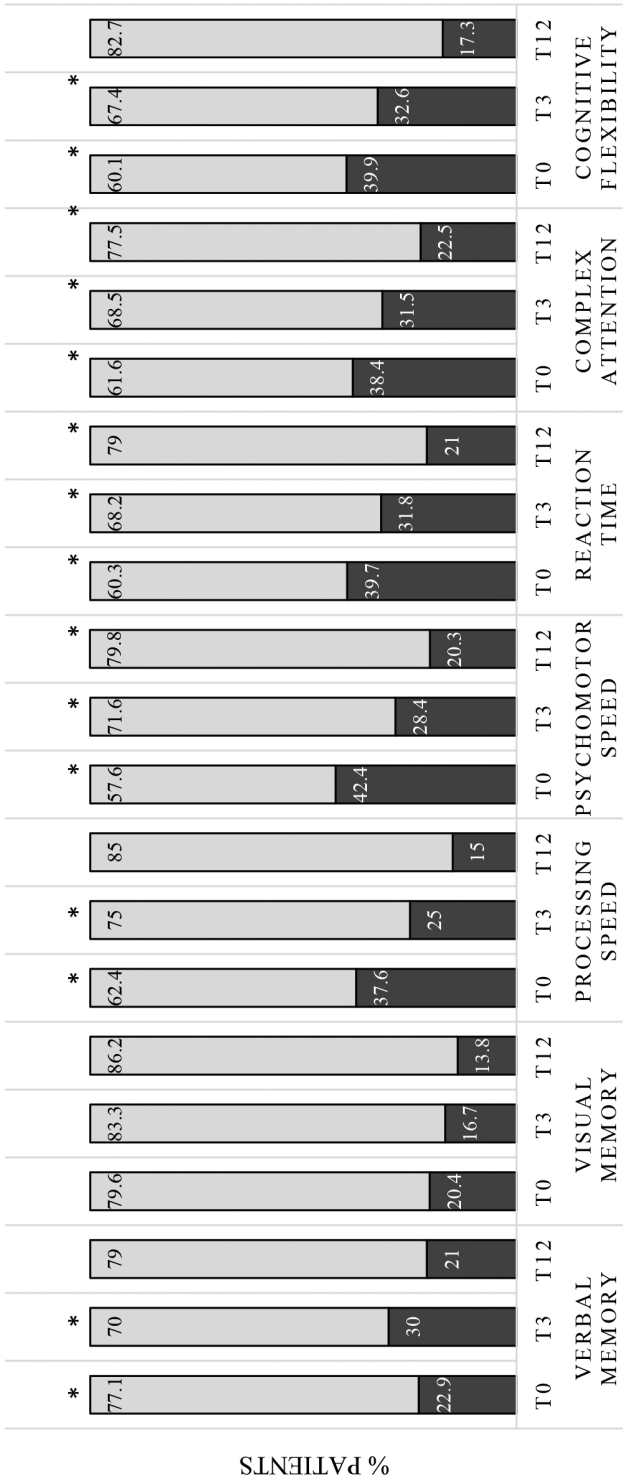


Figure 2 Percentages of meningioma patients with impaired or non-impaired performance over CNS VS cognitive domains at all time-points. The asterisk* indicates impairments that were significantly more frequent in meningioma patients as compared to in normative controls.

Changes in individual and group cognitive performance over time. On the individual level, patients demonstrated improvements more often (ranging from 8% to 28% between T0-T3 and 3% to 30% between T3-T12 over different cognitive domains) than declines (ranging from 3% to 15% between T0-T3 and 1% to 15% between T3-T12) over time (Table 3). To compare, 5% to 6% of the normative sample showed declined performance, and another 5% to 6% showed improved performance over time (i.e., RCI values exceeding ±1.645). Declined performance in patients was for none of the cognitive domains, neither over the first (T0-T3) nor over the second (T3-T12) interval, significantly more frequent than in the normative sample, except for declines on reaction time between T0-T3 (χ^2 (2) = 26.84, p = <.001), and T3-T12 (χ^2 (2) = 28.45, p = <.001). However, improvement of performance occurred significantly more frequently on 6 out of 7 domains over the first interval (i.e., all domains but verbal memory), and 4 out of 7 domains (i.e., verbal memory, reaction time, complex attention, and cognitive flexibility) over the second interval.

Table 3 Changes in cognitive performance of individual meningioma patients

Interval	**T0-T3**			**T3-T12**		
Cognitive domain	declined N (%)	stable N (%)	improved N (%)	declined N (%)	stable N (%)	improved N (%)
Verbal Memory	16 (8%)	175 (84%)	17 (8%)	1 (1%)	61 (78%)	16 (21%)*
Visual Memory	11 (5%)	168 (81%)	29 (14%)*	6 (7%)	69 (90%)	2 (3%)
Processing Speed	6 (3%)	167 (78%)	40 (19%)*	2 (3%)	71 (92%)	4 (5%)
Psychomotor Speed	13 (6%)	142 (66%)	60 (28%)*	6 (8%)	66 (87%)	4 (5%)
Reaction Time	31 (15%)*	132 (62%)	49 (23%)*	12 (15%)*	44 (56%)	23 (29%)*
Complex Attention	24 (11%)	142 (69%)	41 (20%)*	7 (9%)	51 (64%)	21 (27%)*
Cognitive Flexibility	23 (11%)	140 (67%)	45 (22%)*	4 (5%)	51 (65%)	24 (30%)*

* p < BH-corrected alpha .04, compared to proportions of reliable decline, stability and improvement in the normative sample

The final LMEMs demonstrated changes in cognitive performance on the group level, as shown in Table 4. Patients' performance improved significantly over the first time interval on 3 domains. Performance on verbal memory was found to decline significantly (B = -0.22, SE = 0.09, p = .018), and no significant changes in performance were found for visual memory, complex attention, and cognitive flexibility (respectively B = 0.19, SE 0.09, p = .038; B = 0.25, SE = 0.15, p = .095; and B = 0.21, SE = 0.12, p = .079). Over the second interval, significantly improved performance was found for 4 out of 7 domains, no changes were found between T3 and T12 on verbal memory (B = 0.26, SE = 0.13, p = .044), visual memory (B = -0.10, SE = 0.12, p = .398), and psychomotor speed (B = 0.02, SE = 0.09, p = .864). The variability in time between T0 and T12 (i.e., ranging from 8 to 20 months) did not significantly affect late cognitive performance on any of the CNS VS domains (data not shown).

Table 4 Parameter estimates of the LMEMs for pre-operative predictors of late cognitive performance (at T12) on CNS VS domains

	Verbal Memory	**Visual Memory**	**Processing Speed**	**Psychomotor Speed**	**Reaction Time**	**Complex Attention**	**Cognitive Flexibility**
	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)
Interval T0-T3 [a]	**-0.22 (0.09)**	0.19 (0.09)	**0.22 (0.07)**	**0.42 (0.08)**	**0.33 (0.13)**	0.25 (0.15)	0.21 (0.12)
Interval T3-T12 [a]	0.26 (0.13)	-0.10 (0.12)	**0.21 (0.07)**	0.02 (0.09)	**0.49 (0.18)**	**0.49 (0.18)**	**0.53 (0.10)**
Sociodemographic variables							
Age [b]	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	-0.01 (0.01)	-0.02 (0.01)	**-0.02 (0.01)**	-0.00 (0.01)
Sex [b]							
female (vs men)	0.16 (0.19)	-0.44 (0.18)	**-0.50 (0.15)**	0.00 (0.16)	0.30 (0.30)	0.06 (0.19)	0.23 (0.14)
Education [b]							
middle (vs low)	-0.02 (0.20)	0.17 (0.18)	0.07 (0.16)	-0.22 (0.17)	0.22 (0.31)	-0.06 (0.20)	0.01 (0.14)
high (vs low)	0.42 (0.21)	0.10 (0.19)	-0.02 (0.17)	**0.51 (0.18)**	0.42 (0.32)	0.41 (0.21)	-0.22 (0.15)
Clinical variables							
Hemisphere [b]	-0.09 (0.16)	-0.13 (0.15)	-0.12 (0.13)	-0.27 (0.14)	-0.13 (0.25)	0.04 (0.16)	0.20 (0.12)
right (vs left)							
Supratentorial [b]	0.16 (0.29)	0.52 (0.26)	-0.26 (0.23)	-0.37 (0.24)	0.24 (0.45)	0.15 (0.27)	-0.15 (0.21)
yes (vs no)							
Frontal [b]	-0.12 (0.17)	-0.40 (0.16)	-0.21 (0.14)	-0.09 (0.15)	0.18 (0.27)	0.27 (0.17)	0.03 (0.13)
yes (vs no)							

Table 4 Continued

	Verbal Memory	Visual Memory	Processing Speed	Psychomotor Speed	Reaction Time	Complex Attention	Cognitive Flexibility
	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)
Multiple [b]							
yes (vs no)	0.12 (0.35)	0.37 (0.32)	0.14 (0.28)	-0.44 (0.30)	0.26 (0.54)	-0.01 (0.34)	0.16 (0.25)
Volume *mm* [bc]	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
ASA score [b]							
>3 (vs 1 or 2)	0.42 (0.24)	-0.28 (0.22)	0.02 (0.19)	-0.50 (0.20)	-0.08 (0.37)	-0.23 (0.23)	-0.40 (0.17)
Medication [bd]							
yes (vs no)	0.02 (0.17)	-0.19 (0.15)	-0.10 (0.13)	-0.11 (0.14)	-0.30 (0.26)	-0.14 (0.17)	0.11 (0.12)
Psychological variables							
HADS *A* [be]	0.01 (0.02)	-0.05 (0.02)	-0.03 (0.02)	-0.04 (0.02)	0.00 (0.04)	-0.01 (0.02)	-0.00 (0.02)
HADS *D* [be]	-0.02 (0.02)	0.01 (0.02)	0.03 (0.02)	0.03 (0.02)	-0.03 (0.03)	0.01 (0.02)	-0.00 (0.01)
Cognitive variables							
Verbal Memory [b]	-	**0.31 (0.06)**	0.04 (0.06)	0.03 (0.06)	0.09 (0.11)	0.04 (0.07)	-0.07 (0.05)
Visual Memory [b]	**0.39 (0.07)**	-	-0.07 (0.06)	0.04 (0.06)	0.01 (0.11)	0.08 (0.08)	0.06 (0.06)
Processing Speed [b]	0.01 (0.09)	-0.07 (0.08)	-	**0.34 (0.06)**	0.17 (0.14)	0.07 (0.09)	0.14 (0.07)
Psychomotor Speed [b]	0.13 (0.08)	0.08 (0.08)	**0.39 (0.05)**	-	0.17 (0.12)	-0.17 (0.08)	0.05 (0.06)
Reaction Time [b]	-0.01 (0.05)	-0.04 (0.04)	0.01 (0.04)	0.02 (0.04)	-	-0.04 (0.05)	**0.11 (0.03)**
Complex Attention [b]	0.08 (0.08)	0.06 (0.08)	0.03 (0.07)	-0.10 (0.07)	-0.10 (0.13)	-	**0.59 (0.03)**
Cognitive Flexibility [b]	-0.09 (0.11)	0.05 (0.10)	0.18 (0.09)	0.23 (0.09)	0.46 (0.17)	**1.05 (0.05)**	-

[a] in bold: $p <$ BH-corrected alpha .03
[b] in bold: $p <$ BH-corrected alpha .005
[c] data missing for N = 6; [d] data missing for N = 6; [e] data missing for N = 7
Estimates (B) are positive or negative depending on whether they are predicting higher (+) or lower (-) cognitive performance at T12.

Predictors of late cognitive impairment. Table 4 shows the final LMEMs for the cognitive domains of CNS VS. Older age, and cognitive flexibility score at T0 was significantly associated with a lower *Z*-score on complex attention at T12. Male sex and higher T0 psychomotor speed performance were significantly predictive for a higher score on processing speed. A high educational level and better T0 processing speed performance significantly predicted a higher psychomotor speed score. Higher T0 verbal memory performance significantly predicted a higher visual memory score, and vice versa, higher T0 visual memory performance predicted a higher verbal memory *Z*-score. Higher performance on reaction time and complex attention at T0 were significantly predictive of higher cognitive flexibility scores (*p's* < BH-corrected alpha of .005). None of the pre-operatively known clinical or psychological variables were found to significantly predict cognitive performance at T12 (*p's* > BH-corrected alpha of .005).

The former is also reflected by the large proportion of variance explained (i.e., marginal R^2) by the cognitive T0 predictors for the LMEMs. The variance explained ranged from 3% to 14% when only sociodemographic variables were included in the LMEMs as fixed effects, from 5% to 22% when clinical variables were added, from 7% to 22% when psychological variables were added, and from 24% up to 85% when the cognitive variables were added to the models (data not shown).

DISCUSSION

In general, pre-operative cognitive deficits have been documented in patients with meningioma, and a number of studies suggested that patients also show post-operative impairments (2-11). Prospective studies including pre-operative assessments, also including analyses on the individual level, however, are still often lacking.

We found extensive pre- as well as 3- and 12-months post-operative cognitive deficits in our large sample of meningioma patients: mean performance of patients was significantly lower on all cognitive domains at all 3 time-points as compared to the normative sample with predominantly large, but also medium, effect sizes (Cohen's *d* ranging from .35 up to 1.53). On the individual patient level, impairments were significantly more common in meningioma patients on respectively 6 out of 7 cognitive domains at T0 and T3, and 3 out of 7 domains at T12 when compared to normative controls. Performance on psychomotor speed, reaction time, and complex attention was most frequently, as well as most severely, impaired.

The results indicate that cognitive performance improves on the group level over time. Over the first time interval we found significantly improved scores for processing speed, psychomotor speed, and reaction time. Further improved performance was found for processing speed, reaction time, complex attention, and cognitive flexibility over the second time interval. Yet, as it is expected that some patients show improved, and other patients show declined performance over time, mean results of a group may mask changes in performance in individual patients. RCIs showed respectively declined and improved performance in 1 to 15% and 3 to 30% of the patients over the different cognitive domains over the 2 time intervals. However, the proportions of patients with declined performance was for none of the domains, and for none of the 2 intervals significantly larger than in the normative sample, except for declines on reaction time over both intervals (15% of the patients declining between T0-T3, and again 15% between T3-T12). In contrast, improvements were significantly more common in meningioma patients (as compared to the normative sample) for most cognitive domains over the first time interval, and over half of the cognitive domains over the second time interval. Improvements of performance over time were the most frequent and largest for the domains that were most frequently and severely impaired at pre-operative assessment, namely reaction time, psychomotor speed, and complex attention.

It should be noted that post-operative improvements do not imply that performance of patients returns to unimpaired levels: group performance was still significantly lower on all domains as compared to the normative sample, and in addition, about 13% up to almost a quarter of the patients showed impaired performance over different domains at T12.

The LMEMs, conducted in order to identify pre-operative predictors of late cognitive performance, indicated younger age, male sex, and a higher education as predictors of better performance on some domains 12 months after surgery, while sociodemographically corrected *Z*-scores (28) were used. These findings can be partly related to the concept of cognitive reserve that posits cognitive processes, consisting of differences in cognitive efficiency, capacity or flexibility that are shaped by for example education, socioeconomic status and life experiences, as explanation of differences between patients who are functionally impaired and patients who are not despite equal brain pathologies (38-41). The finding of additional predictive effects of age and education, factors that are both associated with cognitive reserve (41, 42), suggest that these variables play a larger role in meningioma patients than in healthy controls. Neither the clinical nor the psychological variables appeared to have significant predictive value for late cognitive performance. Mixed results have been demonstrated in previous studies with regard to the location and volume of meningioma in relation to cognitive performance; whereas some studies demonstrated no significant effects (2), others demonstrated for example more deficits in patients with frontal meningioma or with a relatively large tumor volume (12, 13 , 15 ,20). However, meningioma do not directly damage brain regions but may reduce the functional integrity even of remote brain regions through compression by the tumor (43). Therefore, long-term cognitive deficits are not likely locally-based and consequently, not expected to be pre-operatively predictable by tumor location or volume. Results of the current study also suggest that pre-operative mood (i.e., anxiety and depression) is not a predictor for cognitive outcome. Yet, some (small) associations between mood and cognitive performance after surgery were demonstrated before (9). A pre-operative increase of anxiety and depression can be a very normal reaction to the diagnosis and upcoming major treatment of a meningioma, however, it is not very likely that this increase is also related to late cognitive deficits.

As mentioned previously, the current study has a larger sample size and a longer follow-up (i.e., 12 months versus 3 months) as compared to our previous study (N = 68) (8). CNS VS was assumed to be suitable for serial administration without inducing practice effects at the time of our previous study (9, 27). However, we demonstrated effects of sex and education on CNS VS performance in addition to the known effects of age in the Dutch normative sample, as well as practice effects over repeated assessments (28, 29). It should be noted that the observed severity of cognitive deficits of meningioma patients in our previous study was therefore possibly underestimated, in particular with respect to cognitive flexibility. In addition, improvement due to practice effects may have overwhelmed effects of 'true' change over time, and may have contributed to the observed improvement in test performance in the former patient group, mainly on cognitive flexibility and processing speed (9).

The current study has some limitations that should be noted. We solely included patients who were considered acceptable candidates for surgery and capable of undergoing the pre-operative NPA. Consequently, results may be biased towards an overestimation of cognitive performance in meningioma patients in general. Also, one should take into account that the T12 assessment was (opposed to T0 and T3) no longer part of clinical neuro-oncological care. As this assessment was implemented about 4 years after the start of the study, a significant proportion of the T3 sample (i.e., 33%) dropped-out before T12 as more than 20 months had already passed

since surgery for these patients. A considerably smaller number of patients (21%) dropped-out because they were not motivated to participate. Comparisons of baseline characteristics of the samples included at T0, T3, and T12 suggest that there were no sociodemographic, clinical, and psychological differences between patients who completed the T12 assessment and those who did not. It is therefore unlikely that only a specific group of highly motivated, relatively well-functioning patients was willing to participate in this follow up.

Increasing attention is being paid to rehabilitation in meningioma patients. Recently, positive effects of a 12-week exercise program were suggested on amongst others symptoms of depression and verbal learning in a small group of meningioma patients, although there was no control for practice effects in this study (44). Another study presented positive effects of cognitive rehabilitation in the acute post-operative phase (starting within 1 week after hospital admission) on cognitive performance in neuro-oncological patients (45). Feasibility of and patient satisfaction with an iPad-based cognitive rehabilitation program was recently demonstrated in a small and heterogeneous group of patients with glioma and meningioma (18). A randomized controlled trial on the effects of this program on, amongst others, cognitive performance in a larger sample is currently ongoing (19). The increasing opportunities for rehabilitation of cognitive functions demand knowledge of characteristics of meningioma patients who are at high risk of cognitive deficits after surgery, as presented by the current study.

Although performance improves over time on the group level in our large sample of meningioma patients, the majority of individual patients showed stable cognitive functioning, and cognitive scores still remain significantly lower than in healthy controls up to 12 months after surgery. Our study demonstrates that a pre-operative NPA, together with easily available sociodemographic information, may provide valuable information on the late cognitive outcome of individual meningioma patients. This knowledge can help to inform patients and clinicians on late cognitive status at an early stage. In addition, it emphasizes the need for pre-surgical NPA in meningioma patients, and stresses the need for timely rehabilitation in patients who are at risk for cognitive impairment.

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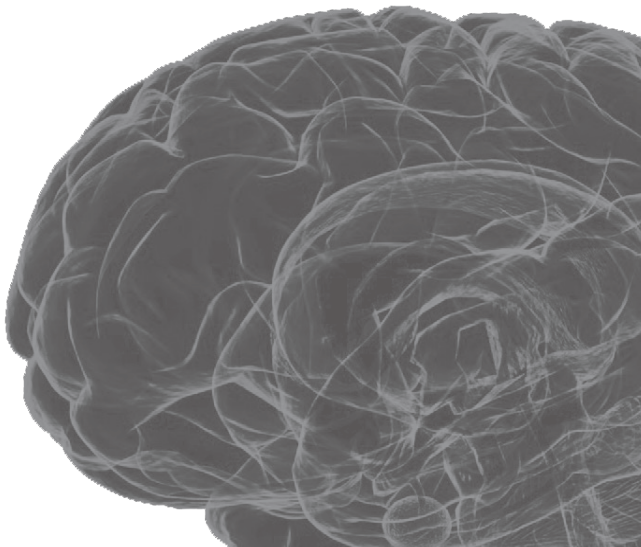
CHAPTER 7

General discussion



SUMMARY

Meningiomas, the most common primary CNS tumors, are in the vast majority of cases benign tumors with a good prognosis. Despite abundant medical reports about surgical techniques, clinical outcome, and long-term survival, relatively little is known about the impact of surgery or other treatments on the course of cognitive functioning over time. Most meningiomas are benign and characterized by slow growth. Many of them remain asymptomatic for a patient's lifetime, or are only discovered incidentally by brain imaging (1). Part of the meningiomas become symptomatic. They may have grown to a considerable size before clinical symptoms appear, presumably due to slow growth and the plastic potential of the brain (2-4). Cognitive deficits can be very subtle and easily go undetected up on routine clinical examination. The aim of this thesis was to evaluate cognitive dysfunction in more detail in meningioma patients, and, more specifically to gain new insights in individual performance, change, and predictors of cognitive performance in meningioma patients before and after surgery. In addition, this thesis also aimed to evaluate computerized testing as a clinical instrument to detect cognitive impairment in meningioma patients.

A systematic review **(Chapter 2)** was done to evaluate the available data and the quality of studies on cognitive impairment in meningioma patients before and after treatment (i.e., surgery with or without adjuvant radiotherapy). Study methods used to evaluate cognitive function in meningioma patients were also reviewed. It was observed that surprisingly few studies (11 publications) had been conducted at that time (2015) on cognitive functioning in meningioma patients. In addition, drawing conclusions from these studies and comparison of results between them was complicated by several methodological limitations, such as a lack of pre-treatment assessments, variations in the number and types of neuropsychological tests used, different definitions of cognitive impairment, low quality of normative data, and absence of control for practice effects (i.e., improvements in performance due to familiarity with the test, its items, and test procedures as opposed to true cognitive improvement). Despite these limitations, the results from the studies reviewed suggest that most of meningioma patients are faced with cognitive deficits in several cognitive domains before surgery. In general, most commonly affected domains were memory, attention, and executive function. Following surgery, most of these patients seem to improve in cognitive functioning, mostly on memory, attention, and executive function. However, they were still left with impairments in a wide range of cognitive functions compared to healthy controls, whereby there is a lack of consistency across studies about the domains that did or did not improve after surgery. A survey of the literature thus indicated that the prevalence of cognitive impairments in meningioma patients is much larger than usually acknowledged on clinical grounds (5). This stresses the relevance of this research project and the need to evaluate cognitive functioning in meningioma patients more thoroughly.

In recent years various computerized neuropsychological test batteries such as CNS VS have been developed that offer an attractive alternative to (often more lengthy) traditional neuropsychological paper-based assessment. Normed scores are automatically generated by CNS VS and represent the performance of an individual relative to the American normative sample controlled for age. We evaluated the first-time use of the formal Dutch translation of the CNS VS battery as computerized clinical neuropsychological screening tool for cognitive function in a (Dutch) neurological patient population (N = 32). Cognitive performance on CNS VS was examined in patients with trigeminal neuralgia (TN) before microvascular decompression (MVD) in comparison with healthy controls. Since the largest neurocenter of the Netherlands is located in the Elisabeth-TweeSteden Hospital, we had access to a relatively large group of these patients. In addition, no information was available on cognitive performance in TN patients as no prior

studies had been conducted, which prompted us to start our research project with this particular patient group. Our pilot study showed that patients with TN scored significantly lower than the American normative sample on 5 out of 5 selected cognitive domains (i.e., composite memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility). Comparisons between patients and a small control group of Dutch subjects (N = 20) tested with the same battery revealed quite the same pattern of differences in mean test performance. We concluded that a brief computerized neuropsychological assessment can be a practical alternative for lengthy traditional neuropsychological testing in the clinical research setting, and that patients with TN need to be carefully evaluated for cognitive deficits **(Chapter 3)**.

The major aim of this research project was to evaluate cognitive function in meningioma patients with computerized tests. Data from 68 meningioma patients was collected in a prospective study in which patients were neuropsychologically tested before and 3 months after surgery. In line with previous studies with conventional (i.e., paper and pencil) neuropsychological tests, meningioma patients demonstrated significantly lower scores on all 7 cognitive domains (i.e., memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, and executive functioning) before surgery. After surgery we observed significant improvements on 5 out of 7 domains at group level (i.e., memory, complex attention, cognitive flexibility, processing speed, and executive functioning). For psychomotor speed and reaction time, no significant improvement was observed. As psychomotor speed and reaction time were less impaired than other cognitive domains at baseline (i.e., before surgery), this may have left less room for improvement. However, group performance was still significantly lower on all domains as compared to the American normative sample. At the individual level, we found that respectively 69% and 44% of the patients scored lower than 1.5 *SD* below the mean of the American normative sample on at least 1 cognitive domain pre- and post-operatively. As no 2 presentations of CNS VS are similar due to the random presentation of stimuli, the battery was assumed to be suitable for serial administration without inducing practice effect (6). Therefore, there seemed to be no need to correct for practice effects. Our study again suggested that a rapid, efficient and cost-effective computerized neuropsychological test battery is a good alternative for conventional, lengthy neuropsychological testing **(Chapter 4)**.

As CNS VS' normative data collected in an American population were established over a decade ago, with corrections for age only, the applicability of the original CNS norms and effects of other sociodemographic variables on cognitive performance was examined in a healthy Dutch sample (N = 158). The Dutch sample showed better performance on CNS VS as compared to that of the American normative sample on the 2 domains covering different types of speed (psychomotor speed and processing speed) as well as on cognitive flexibility. In addition, effects of education and sex on CNS VS performance were identified in the Dutch sample and should therefore be taken into account when cognitive performance is evaluated in individual patients. Based on these data, we established regression-based normative formulae to adjust for the effect of sociodemographic variables on performance on CNS VS. In future evaluations of performance in our (Dutch) patient studies, and also in clinical practice at the Elisabeth-TweeSteden Hospital, these normative data will be used instead of the American norms **(Chapter 5)**. Below we will discuss the implications of these findings for the results described in Chapter 4.

Final analyses **(Chapter 6)** were conducted to investigate individual changes in cognitive performance over time and predictors of late cognitive functioning in meningioma patients after surgery. This study has a larger sample size and a longer follow-up (i.e., 12 months versus 3 months) as compared to our previous study (N = 68; Chapter 4). At the pre-surgery time-point,

261 patients were assessed, and 229 and 82 patients were retested 3 and 12 months after surgery respectively. In accordance with are previous study (N = 68; Chapter 4) we found significantly lower performance in patients on all (7 out of 7) cognitive domains at all 3 time-points as compared to our Dutch normative sample (N = 158). Although cognitive performance improved at the group level, the majority of individual patients showed stable cognitive functioning over time. In addition, group performance was still significantly lower on all domains as compared to the normative sample. Unlike in our previous study, we corrected for practice effects since we applied Reliable Change Index (RCI) formulae for the determination of reliable change in CNS VS' domain scores, based upon results on repeated assessments of CNS VS in the same Dutch normative sample as described above (N = 158, N = 131, N = 77 at baseline, at 3-months and 12-months follow-up) (6). The implications of these correction for practice effects for the results described in Chapter 4 will be discussed below. In addition, we found that pre-operative performance predicted late cognitive performance, and that lower age, male sex, and higher educational level were found to predict better cognitive performance 12 months after surgery. These results can help to inform patients and clinicians on late cognitive status at an early stage, and emphasize the need for cognitive rehabilitation when necessary. Patients whose cognitive performance is already impaired before surgery are at risk of having late cognitive deficits: this stresses the need for implementing (pre-operative) neuropsychological assessments into the clinical care of meningioma patients.

METHODOLOGICAL CONSIDERATIONS

The findings of the studies described in this thesis need to be considered in the context of the methodological merits and limitations of this project.

Although the studies in this thesis provide us with evidence to apply CNS VS as a brief computerized neuropsychological battery to evaluate cognitive function in patients with meningioma, some limitations concerning the use of CNS VS should be noted. The results from the pilot study in patients with TN (N = 32) at that time led us to use CNS VS' normative database in our prospective study on the incidence and severity of cognitive dysfunction in meningioma patients before and 3 months after surgery (7) (Chapter 4). In this study, patients' cognitive scores were comparable to the original American CNS VS norms. However, a possible Flynn effect should be considered given the headspring of the normative data presented by CNS VS (i.e., the original peer reviewed reliability and validity paper was published in 2006 (6)). The Flynn effect refers to a substantial rise of the population's performance on tests of intelligence in developed countries, typically about 3 to 5 points per decade (i.e., on a IQ scale with a mean of 100 and standard deviation of 15 points) (8, 9). Since 2006, the normative database has been expanded to over 1,900 participants, but unfortunately no information on the updated CNS VS normative database has been reported to date. As a result, there is no publicly available description of the composition of the American sample regarding background characteristics, nor the basis on which participants were classified as "normal," except that they had "no past or present neurological or psychiatric disorder, head injury, and learning disabilities" (10). Another limitation of the original CNS VS' normative data concerns the absence of adjustments for effects of education and sex, as normalized scores are solely age-corrected. Age, education, and to a lesser extent sex have extensively been found to correlate with performance on numerous neuropsychological tests (11), including performance on computerized tests (12-14). As described in Chapter 5, we found that Dutch participants (N = 158) showed higher scores on 3 out of 7 cognitive domains (i.e., processing speed, psychomotor speed, cognitive flexibility) as compared to the American normative sample. In addition, effects of education and sex on CNS VS performance were also identified in the Dutch

sample (N = 158). Therefore, it should be noted that, as described in Chapter 4, the observed severity of cognitive deficits in our prospective study of meningioma patients (N = 68), was possibly underestimated in these patients, in particular with respect to cognitive flexibility.

In addition, despite the fact that CNS VS is assumed to be suitable for repeated testing without inducing practice effects[1] due to the random presentation of stimuli, there still could be a learning effect of the battery in general i.e., performance gain at retest due to familiarity with, and recognition of, test materials and procedures (16). In addition, our follow-up study on test-retest reliabilities and practice effects for CNS VS demonstrated that Dutch healthy participants scored significantly higher on the domains of cognitive flexibility, processing speed, and reaction time at the 3-month retest compared to the first assessment. No significant differences in performance were found between the second and third assessment (17). Consequently, improvement due to practice effects may have initially overwhelmed effects of change over time, and may have contributed to the observed improvement in test performance in our patient group (N = 68; Chapter 4) mainly on cognitive flexibility and processing speed, as described in Chapter 4. In addition, as described in Chapter 6, RCIs with correction for practice effects (in addition to the sociodemographic corrections (17)) demonstrated that the majority of individual patients (ranging from 62% to 84%) showed stable cognitive functioning over time. RCIs showed respectively declined and (more often) improved performance in 1 to 15% and 3 to 30% of the patients over the different cognitive domains. We conclude that the observed improvements in our first patient study (N = 68; Chapter 4) merely reflect practice effects, in particular with respect to cognitive flexibility.

Furthermore, we are aware that for some patients computerized testing is more difficult than for others, for example for older patients who are not familiar with computers (18). Iverson and colleagues (19) found that people with 'frequent' computer use performed better than people with 'some' computer use on tests requiring rapid visual scanning and keyboard work. It should be noted that computer skills - including keyboard work and on-screen visual scanning - have improved tremendously over the past decade, which may result in improvements in overall performance on computerized neuropsychological speed tests. As can be expected from the more frequent use of computers nowadays, our Dutch sample (N = 158) comprised too few participants with only some or none computer familiarity to look into these effects. The beneficial effects of computer familiarity may (partly) explain the differences between the American 2006 group and the Dutch 2016 group (20).

With regard to the tests by CNS VS, a closer inspection shows that the verbal memory test (VBM) and the visual memory test (VIM) are actually recognition tests, not tests of recall (6). Since recognition is a response to a sensory cue and recall is the retrieval of information from memory without a cue, recognition can be expected to be easier than recall (21). As a result, we expect performance on recall tests to be more impaired in meningioma patients as compared to recognition tests, and even worse as compared to healthy participants. Therefore, patients' performance on the memory domain may be underestimated in our studies.

1. Practice effects are improvements in performance due to familiarity with the test, its items and test procedures, mimicking true cognitive improvement (14).

CNS VS' cognitive domains show considerable overlap with other domains of the battery (i.e., composite memory, executive functioning, simple attention, and motor speed), and therefore we did not consider all 11 cognitive domains in our analyses.

A note with regard to our selection of meningioma patients should be mentioned (Chapters 4 and 6). Our sample mainly consisted of patients with a meningioma with a diameter > 3 cm, as our hospital tends to adopt a wait-and-scan approach in patients with a smaller meningioma or treat them with Gamma Knife radiosurgery (i.e., a very precise form of therapeutic radiotherapy as alternative to traditional brain surgery and whole brain radiation therapy). Performance in our study population may therefore be slightly worse than performance in the general population of symptomatic meningioma patients. On the other hand, patients with large tumors and patients who were unable to undergo the neuropsychological assessment due to severe visual, motor, or cognitive problems, were excluded from analyses. This selection bias may therefore have resulted in a better performance of this group of meningioma patients.

Despite these given the methodological considerations and limitations of the studies presented in this thesis, this research project is unique in evaluating cognitive deficits in meningioma patients with a brief computerized test battery, in combination with the acquired insights in individual performance, change, and predictors of cognitive performance after surgery. The limited data available on the cognitive outcomes in these patients at the start of this project have emphasized the importance to thoroughly evaluate cognitive functioning in meningioma patients both in research and clinical practice.

CLINICAL IMPLICATIONS AND SUGGESTIONS FOR FUTURE RESEARCH

The studies presented in this thesis provide evidence for cognitive deficits in patients with meningioma before and 3 months after surgery, both at group and individual patient level, which tend to persist during the first year after surgery. Improvements in cognitive performance were somewhat more common than declines, but only a relatively small number of meningioma patients showed changes from pre- to post-operative assessment. Pre-operative cognitive performance of meningioma patients turned out to be the most predictive variable for late cognitive performance, whereas sociodemographic, clinical, and psychological variables were not -or only to very limited degree- predictive for cognitive outcomes. Surgery generally had a beneficial effect on cognitive functioning.

Anxiety and depression symptoms as emotional reactions to diagnosis and prognosis may also have a negative impact on cognitive functioning in meningioma patients (22). However, no clear relationship was found with respect to the psychological aspects of having a brain tumor and its influence on cognitive functioning. As described in Chapter 4, no statistically significant correlation between pre-operative anxiety and pre-operative cognitive functioning was found. On the other hand, there was a negative association of pre-operative depression with pre-operative cognitive function. Future research will help to better define the influence of preexisting depression with cognitive dysfunction after surgery. In addition, as described in Chapter 6, pre-operative anxiety and depression did not predict late cognitive outcome. A pre-operative increase of anxiety and depression can be a very normal reaction to the diagnosis and upcoming major treatment of meningiomas and may have affected pre-operative cognitive function. However, it is not likely that this increase is also related to late cognitive deficits. Surprisingly, neither the clinical nor the psychological variables appeared to have significant predictive value for late cognitive performance.

Other variables such as ineffective coping strategies (e.g., denial or passive coping) of patients who experience stress related to their medical condition may put patients at risk for cognitive dysfunction. Differences in coping strategies may serve as an indirect explanation for the inter-individual differences in cognitive performance that exist among meningioma patients. In patients with non-CNS cancers, coping was found to be a significant mediator of the relationship between stress and neuropsychological outcomes, confirming that active coping was one mechanism that linked cancer stress and (better) neuropsychological outcomes (23-25).

In addition, evidence also suggests that germline mutations and tumor genetic factors may affect (individual differences in) the development of cognitive impairment in primary brain tumor patients (26). Our research group is currently investigating the role of the apolipoprotein *E (ApoE)* ε4 allele in the explanation of individual differences in cognitive performance in a large sample of patients with meningioma and glioma. In other populations, including traumatic brain injury and stroke, *ApoE* status is known to influence neurocognitive outcome (26).

Based on the results of these studies, clinicians and patients can be better informed about cognitive dysfunction and should be aware of this risk in meningioma patients. As mild or moderate cognitive impairments are insufficiently detected with routine medical examinations, we propose that meningioma patients should be routinely evaluated with neuropsychological testing when they are admitted for brain surgery. For this purpose, a brief computerized neuropsychological assessment such as CNS VS (6) can be a practical alternative for traditional neuropsychological testing. Since CNS VS' cognitive domains show considerable overlap with other domains of the battery, we suggest not to consider all 11 cognitive domains in analyses. Diagnosis and treatment of these cognitive deficits are expected to improve outcomes and quality of life in meningioma patients by timely providing appropriate care (for example cognitive rehabilitation (27, 28)).

As a spin-off of the current study new research questions regarding meningioma patients have developed since then, for example on the impact of cognitive deficits on work functioning, community integration and subjective cognitive complaints. Our group also explored the relationship between tumor location and cognitive functioning in meningioma patients (29). Also, an iPad-based cognitive rehabilitation program for our meningioma patients was developed (30). All these studies were established within the department of Neurosurgery of the Elisabeth-TweeSteden Hospital (Tilburg, The Netherlands) together with department of Cognitive Neuropsychology of Tilburg University.

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